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RESPONSES OF THE HUMAN POST-PARTUM UTERUS TO POSTERIOR PITUITARY EXTRACTS*

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INTRODUCTION

OLIVER and Schafer[1] (1894) demonstrated that a preparation of the posterior pituitary gland caused an elevation of blood pressure. Dale[2] (1906) and Blair-Bell and Hicks[3] (1909) demonstrated that an oxytocic effect could be produced by an extract of the posterior pituitary gland. Shortly thereafter, posterior pituitary preparations were introduced as oxytocic drugs for clinical use. Kamm and his associates[4] (1928) claimed an almost complete separation of the oxytocic and pressor principles from pituitary extract and made these two factors available for physiologic and pharmacologic study and for clinical use. The oxytocic fraction was called pitocin and the pressor fraction, pitressin.

A review of the literature[5-14] revealed that very few investigators have studied the responses of the uterus of the laboratory animal to these substances in the immediate post-partum period. Many clinical investigators advocate the use of posterior pituitary extracts to control post-partum bleeding, but only a few have recorded kymographic tracings of the reactions of the human post-partum uterus to these preparations. Bourne and Burn[15] recorded uterine activity by means of a hydrostatic bag inserted 8 cm. above the cervical os in a patient during labor. They found that pitressin, even in large doses, produced no oxytocic effect while pitocin caused increased and sustained activity. Adair and Davis[16] administered pituitrin, pitocin, and pitressin intravenously to women immediately post partum and recorded the uterine activity by means of an intrauterine bag. Their tracings indicated that

*This study was aided in part by a grant from the Faculty Research Fund.

there was no essential difference in the effect of these three preparations on the human post-partum uterus. As pointed out by Weinstein and Friedman,[17] Adair and Davis did not investigate the possibility that the dose of pitressin administered might contain sufficient amounts of the oxytocic principle to produce a response in the extremely sensitive post-partum uterus. Moir[18] demonstrated by kymographic tracings that pituitary extracts injected subcutaneously produced a rapid and definite oxytocic action in the post-partum patient.

Commercial extracts are prepared from the posterior pituitary gland of the ox and are standardized briefly as follows: The oxytocic fraction is assayed in vitro on muscle strips from the uterus of the virgin guinea pig. The vasopressor fraction is assayed in vivo by its effectiveness in elevating the blood pressure when injected intravenously into an anesthetized dog. One milligram of the International Standard Powder represents about 7 mg. of fresh posterior lobe (ox) and contains 2 International Units of the oxytocic substance (Van Dyke, 1936).[19] There is no international pressor unit. Parke, Davis and Company have adopted a method of comparing the pressor effect of posterior pituitary extracts with known standards. This activity has been expressed in pressor units.

The amounts of the oxytocic and pressor factors in the Parke, Davis and Company extracts are as follows (Kamm).[20]

AMOUNT	INTERNATIONAL OXYTOCIC UNITS	PRESSOR UNITS
Pituitrin 1 c.c.	10	5-10
Pitocin 1 c.c.	10	Traces
Pitressin 1 c.c.	Traces	10 or 20

METHODS

Normal post-partum patients were selected on the sixth to ninth days after delivery. Following the method of Adair and Davis, a 10 c.c. Hagner bag was inserted, under sterile precautions, into the uterine cavity and was attached by a water system to a recording mercury manometer. Kymographic tracings of uterine activity were recorded when posterior pituitary extracts were injected either intravenously or subcutaneously. This method of study has been carried out on 200 patients and no deleterious effects have been noted. This paper deals only with the results obtained from the intravenous injection of posterior pituitary substances.

Solutions of pituitrin, pitocin, and pitressin were used. There was considerable individual variation in the responses of different patients to similar doses of the same drug. To rule out this individual variability, it was deemed necessary to compare the oxytocic effect of each of the three posterior pituitary extracts on each patient. The sequence of administration was varied to avoid any induced tolerance or sensitivity due to a previously administered drug. Twelve patients were studied in this manner (Table I). The dose was 0.3 c.c. in each instance because this was found to be the maximum amount of pitressin (3 pressor units) that could be given intravenously without causing undue pressor symptoms. Kymograph tracings were made for fifteen to thirty minutes prior to the injection of a preparation to determine the character of any spontaneous uterine activity. The interval between injections varied from thirty to sixty minutes and at least ten minutes was allowed

TABLE I. SEQUENCE OF ADMINISTRATION OF THE POSTERIOR PITUITARY EXTRACTS

NO. OF PATIENTS	FIRST DRUG	SECOND DRUG	THIRD DRUG
2	Pitocin	Pitressin	Pituitrin
2	Pitocin	Pituitrin	Pitressin
2	Pitressin	Pitocin	Pituitrin
2	Pitressin	Pituitrin	Pitocin
2	Pituitrin	Pitocin	Pitressin
2	Pituitrin	Pitressin	Pitocin

to intervene between the cessation of activity induced by one preparation and the injection of the subsequent posterior pituitary extract.

Representative tracings of the responses of 5 patients in this group are shown in Fig. 1. There was very little spontaneous uterine activity preceding the first injection in any of these patients. In every instance the initial contraction appeared within ten to twenty seconds after the drug was injected. Individual variations of the responses occurred, but the general characteristics of the tracings were quite similar.

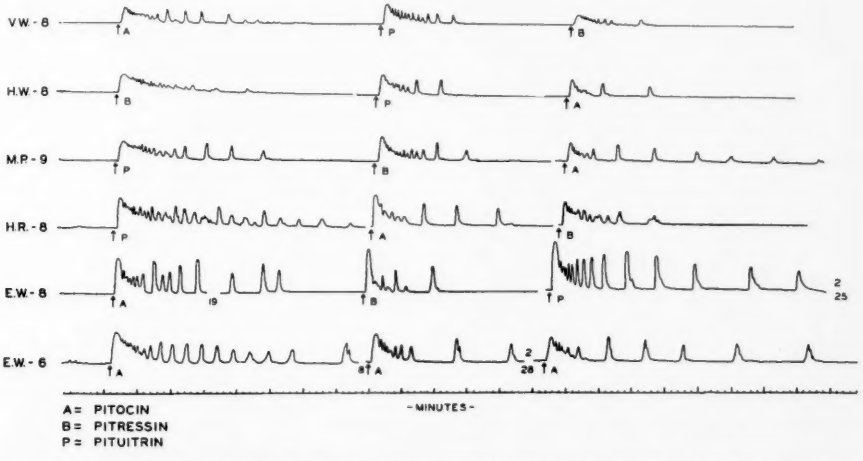

Fig. 1.—Kymograph tracings showing uterine responses to the intravenous administration of pitocin, pitressin, and pituitrin. The dose was 0.3 c.c. in each instance. The tracings have been arranged so that times of injection coincide on the time scale. The legend at the left of each tracing indicates the patient's initials and the day post partum. The numbers below the curve show the interval of time in minutes not shown on the tracing; those above the curve show the number of contractions during this interval. E.W.6 received three repeated injections of pitocin. E.W.6 and E.W.8 are different patients.

An analysis of the characteristics of these tracings further confirmed the similarity of the responses. The average values for the characteristics of the responses of all 12 patients are given in Table II. The average height of the initial contraction, the number of contractions during the first ten minutes, and the duration of the tonus were quite comparable for pitocin, pitressin, and pituitrin. Pitressin appeared to have a somewhat shorter effect.

These same characteristics were averaged according to the sequence of administration of the three preparations as shown in Table III. (The sequence is shown in Table I.) There was a decrease in the number of contractions in the first ten minutes and a decrease in the duration of tonus following the second and third drugs. These figures indicated a nonspecific decreased response to the second and

third drugs. To determine whether the diminished reaction would occur if the same drug were given repeatedly, three successive doses of pitocin were administered to a patient (E. W., 6 Fig. 1). The decreased reaction, especially to the second injection was quite marked. The fact that oxytocic activity of pitressin appeared so much like that of pitocin suggested two possibilities: first, that the human post-partum uterus may be so sensitive to posterior pituitary substances that it responds to the small fraction of the oxytocic substance in pitressin; or second, that there may be a marked species difference in sensitivity to these drugs. If the response of the human uterus were due to the small fraction of oxytocic substance present in pitressin, then it would be possible by equivalent quantitative dilutions of pitocin and pitressin, to find a dilution level at which pitocin would evoke a uterine response but at which level pitressin would not be effective. Dilution studies were made to test this possibility.

Table II. Average Values for the Characteristics of the Uterine Responses to the Intravenous Administration of 0.3 c.c. of Pituitrin, Pitocin, and Pitressin

DRUG	NO. OF CASES	HT. INITIAL CONTRACTION MM.	CONTRACTIONS 1ST 10 MIN.	DURATION OF TONUS MIN.	TOTAL DURATION OF EFFECT MIN.
Pituitrin	12	27.5	12.3	6.6	31.5
Pitocin	12	28.1	10.3	4.8	35.1
Pitressin	12	28.9	12.6	5.8	20.0

Table III. The Average Values for the Characteristics of the Uterine Responses According to Sequence of the Intravenous Administration of 0.3 c.c. of Pituitrin, Pitocin, and Pitressin

DRUG	NO. OF CASES	HT. INITIAL CONTRACTION MM.	CONTRACTIONS 1ST 10 MIN.	DURATION OF TONUS MIN.	TOTAL DURATION OF EFFECT MIN.
First drug	12	29.9	15.0	7.6	33.1
Second drug	12	29.4	10.7	5.0	22.2
Third drug	12	25.2	9.5	4.6	31.3

DILUTION STUDIES OF PITOCIN AND PITRESSIN

Especially assayed preparations of pitocin and pitressin were employed. The pitocin contained 10 International Oxytocic Units and 0.4 pressor units per c.c.; while each cubic centimeter of pitressin contained 0.4 International Oxytocic Units and 10 pressor units. These extracts were diluted with sterile normal saline solution in a range from 1:10 to 1:1,000. These preparations were given intravenously to 60 post-partum patients selected in the same manner as in the first part of the study.

In the first group, injections of 1 c.c. of equivalent dilutions of pitocin and pitressin were given to the same patient at approximately thirty-minute intervals, at least ten minutes elapsing between the cessation of activity caused by the preceding drug and the administration of the succeeding preparations. Again the sequence of treatment was varied to avoid any induced tolerance of sensitivity due to the previously injected drug. It is obvious from the tracings (Fig. 2) that almost identical effects were produced by comparable dilutions of pitocin and pitressin despite their wide difference in oxytocic values. Both preparations were usually ineffective at dilutions greater than 1:100.

A second group of patients were given dilutions of pitocin and pitressin, representing equivalent oxytocic activity. Although the oxytocic values were equivalent by the guinea pig assay method, the reactions of the human post-partum uterus were decidedly different (Fig. 3). Uniformly, the pitressin elicited a greater response

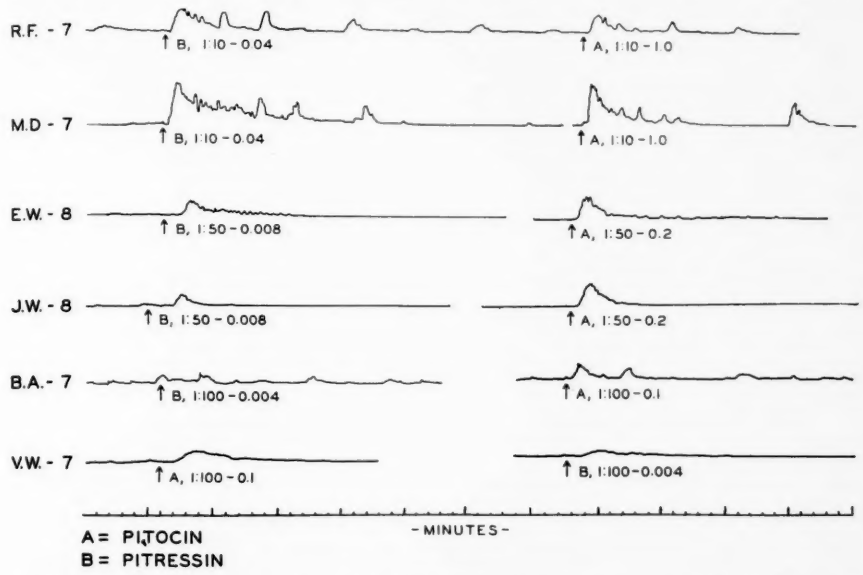

Fig. 2.—Kymograph tracings showing the responses to comparable dilutions of pitocin and pitressin. According to the guinea pig assay, the oxytocic value of pitocin was 25 times more potent than pitressin. The legend under each curve indicates: posterior pituitary extract, dilution of the preparation, the oxytocic potency in International Units. The dose was 1.0 c.c. intravenously, in each instance.

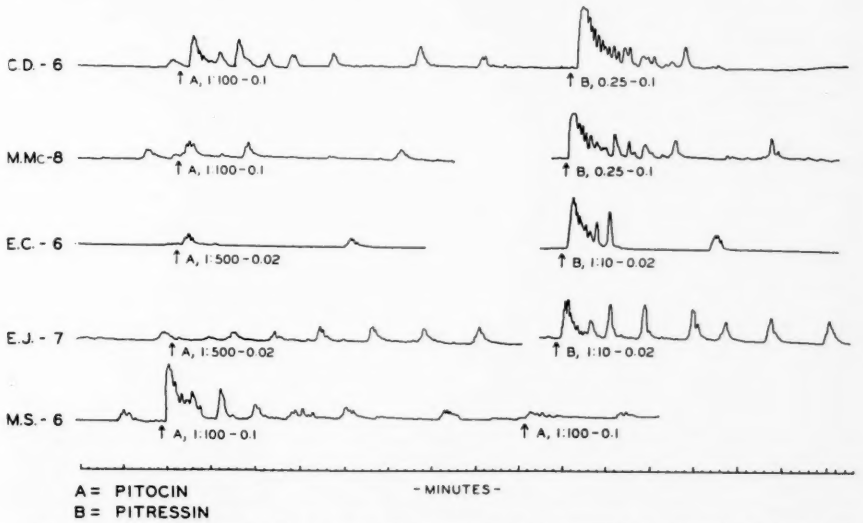

Fig. 3.—Kymograph tracings showing responses of the human post-partum uterus to intravenous doses of pitocin and pitressin which were equivalent in oxytocic values according to guinea pig assay. The legend under each curve indicates: posterior pituitary extract, the dilution of the preparation, the oxytocic potency in International Units. The dose was 1.0 c.c. in each instance, except in the second administration to C.D. 6 and M.Mc. 8, in which the dose was 0.25 c.c. of the undiluted preparation of pitressin.

than did pitocin. The greater response to pitressin when given as the second drug is more significant in view of the fact that results with large doses have shown that the second and third injections were not as effective as the first. The diminished effectiveness of a second injection was demonstrated when two small doses of pitocin were given to the same patient (shown in the tracing of M. S. –6, Fig. 3).

Table IV shows the positive, questionable, and negative uterine reactions in 96 different administrations of the various dilutions of pitocin and pitressin in 60 post-partum patients. The distribution of the responses for pitressin and pitocin could almost be superimposed, showing that similar dilutions exert similar oxytocic effects despite the wide differences in their oxytocic potency as expressed in International Units. According to the guinea pig assays, the pitocin was 25 times more potent as an oxytocic than pitressin, yet, in the human, similar dilutions of pitocin and pitressin were found to evoke similar uterine responses. The minimal effective dose of pitocin and pitressin was found to be about 1 c.c. of a 1:100 dilution of either extract.

An analysis of the characteristics of uterine reactions to the various dilutions of pitocin and pitressin is given in Table V. The height of the initial contraction varies. In some instances the greater dilutions stimulated a greater initial contraction, but all were less than those which followed the large doses. The number of contractions in the first ten minutes and the duration of tonus were similar in all the dilutions as well as in the large doses. These two characteristics seem to be typical manifestations which occur when the uterus responds to the posterior pituitary extracts, regardless of the dose administered. Large doses of pitocin produced a longer total duration of effect than did small doses. Conversely, there was a gradual increase in total duration of effect with higher dilutions of pitressin; the oxytocic effects of the small doses of pitressin were consistently longer in duration than for the larger doses.

TABLE IV. SHOWING THE POSITIVE, QUESTIONABLE, AND NEGATIVE UTERINE RESPONSES IN 96 DIFFERENT INTRAVENOUS ADMINISTRATIONS OF THE VARIOUS DILUTIONS OF PITOCIN AND PITRESSIN IN 60 POST-PARTUM PATIENTS. THE DOSE WAS 1.00 C.C. IN EACH INSTANCE

DILUTION	PITOCIN				PITRESSIN			
	INT. UNITS OXYTOCIC	+	±	–	INT. UNITS OXYTOCIC	+	±	–
1:10	1.0	8			0.04	11	1	
1:50	0.2	8	2	1	0.008	3		3
1:100	0.1	12	2	5	0.004	9	3	5
1:500	0.02	1	1	9	0.0008			3
1:1000	0.01			4	0.0004		1	4

TABLE V. AVERAGE VALUES FOR THE CHARACTERISTICS OF THE UTERINE RESPONSES TO INTRAVENOUS ADMINISTRATION OF 0.3 C.C. OF UNDILUTED (TABLE II) AND 0.1 C.C. OF DILUTED PITOCIN AND PITRESSIN (THE DILUTION FIGURES ARE THE AVERAGE OF THE POSITIVE RESPONSES IN TABLE IV)

DILUTION	HT. INITIAL CONTRACTION MM.		NUMBER CONTRACTIONS 1ST 10 MIN.		DURATION OF TONUS MIN.		TOTAL DURATION OF EFFECT MIN.	
	A*	B	A	B	A	B	A	B
Undiluted	28.1	28.9	10.3	12.6	4.8	5.8	35.1	20.0
1:10	15.0	21.2	9.7	14.9	4.9	7.3	22.7	33.0
1:50	15.0	9.7	9.6	13.0	3.5	3.5	15.2	31.0
1:100	20.0	13.0	10.6	12.0	3.8	5.0	26.3	37.9

*A, Pitocin; B, pitressin.

With the exception of the difference noted in the total duration of effect, there was no marked difference in the oxytocic activity of the equivalent dilutions of pitocin and pitressin. Therefore, the oxytocic effect of large doses (0.3 c.c.) of pitressin on the human uterus is not due to the small amount of the oxytocic factor as determined by guinea pig assay, but is due to the fact that pitressin itself is oxytocic in the human being. The explanation of the contrasting results obtained when these drugs are administered to the post-partum human patient and to the laboratory animal must be based on a species difference in response to pitressin.

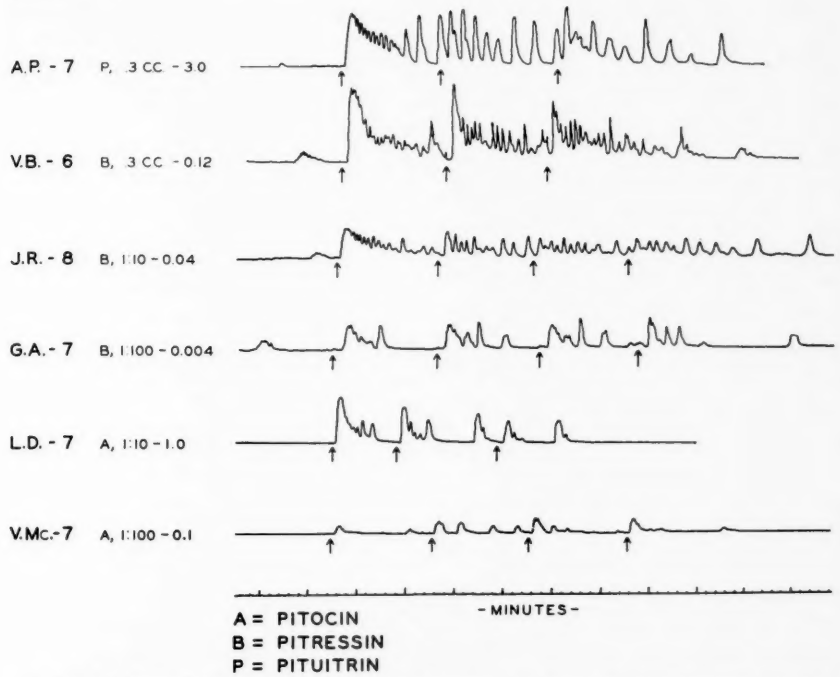

Fig. 4.—Kymograph tracings showing responses to repeated intravenous doses of pitocin, pitressin, and pituitrin. Legends at the left of the curves indicate in order: initials of patients, day post partum, posterior pituitary extract, amount of undiluted preparation or specific dilution, oxytocic potency of the extract in International Units. In the first two patients, 0.3 c.c. of the undiluted preparations was used, while in the remainder, the dose was 1.0 c.c. of the diluted extract as noted in the figure.

Further manifestations of species differences are also evident in this study. In experiments on the laboratory animals, it was found necessary to use a uterus that exhibited spontaneous or induced rhythmic activity in order to carry out studies with posterior pituitary extracts. In the post-partum patients many of the uteri showed no evidence of activity after insertion of the bag, yet an active response to the extracts was obtained. Most of the results on those patients with spontaneous rhythmic uterine contractions were not clear-cut and were difficult to interpret.

REPEATED INTRAVENOUS INJECTIONS OF POSTERIOR PITUITARY EXTRACTS

Weinstein and Friedman showed that large doses of pitressin had an inhibiting effect on spontaneous or induced uterine activity in rabbits.

During this period of inhibition the uterus of the rabbit would not respond to subsequent doses of pitocin. They also found that after the initial oxytocic effect of pituitrin, there occurred a state of uterine inactivity which was due to the pitressin fraction present in the pituitrin. In our experiments, large doses of pituitrin and pitressin stimulated contractions of the human uterus, and there was no evidence of an inhibition of uterine activity. Furthermore, large doses of pituitrin or pitressin repeated every ten minutes caused definite and sustained uterine activity following each injection (see Fig. 4, first 2 tracings). These two tracings also demonstrated a decrease in response to the subsequent injections of large doses of any of the three pituitary extracts. There was no cumulative effect or increased sensitivity when these substances were given at frequent intervals.

Weinstein and Friedman found that small doses of pitressin, while producing no active inhibition of spontaneous uterine activity in the rabbit, did render the uterus refractory for a period of time to subsequent doses of pitocin. In the present study repeated injections of dilutions of pitocin and pitressin were administered to a number of patients (see Fig. 4, last 4 tracings). On each occasion the uterus responded to small doses of pitressin in a manner similar to that of pitocin. Amounts of pitressin less than the minimal effective doses produced no change in spontaneous or induced uterine activity. There was no evidence that these small amounts produced a state of tolerance which rendered the uterus refractory to subsequent doses of pitocin.

DISCUSSION

Factual observations regarding the pressor effects of the various dilutions of the posterior pituitary extracts used in this study were not recorded. The impressions gained during the progress of the work suggest that the pressor factor has been largely separated from pitocin. Only a few of the patients given large doses of pitocin had pressor symptoms. Patients given smaller doses of pitocin never experienced any pressor manifestations whereas those receiving comparable doses of pitressin frequently complained of pressor effects.

From assay studies on a large number of patients, it has been concluded that 1 c.c. of a 1:100 dilution of either pitocin or pitressin is the minimal dose which will cause a definite oxytocic response in the majority of cases. On this basis, a human oxytocic unit might be defined as the smallest amount of posterior pituitary extract given intravenously which produces a definite effect as recorded by an intrauterine bag in the human uterus on the sixth to the ninth post-partum day. In our experience this human unit is approximately 0.01 c.c. of pituitrin, pitocin, or pitressin (Parke, Davis) and is equivalent to 0.1 International Oxytocic Unit.

There was no appreciable difference between the uterine responses on the sixth and the ninth days post partum to large intravenous doses (0.3 c.c.) of the three posterior pituitary extracts studied. The characteristics of our kymograph tracings were very comparable to those obtained by

Adair and Davis in their studies on the post-partum uterus in the first few hours following delivery. Thus, we believe that the results obtained in this investigation may be applied to patients in the immediate post-partum state.

CLINICAL APPLICATION

This study would indicate that when posterior pituitary extracts are given intravenously to combat post-partum hemorrhage, the initial tetanic contraction of the uterus may be anticipated within ten to twenty seconds. While uteri vary in their degree of response to posterior pituitary extracts, the induced activity usually lasts for a period of about thirty minutes. Subsequent intravenous doses are less effective than the first. Failure of the post-partum uterus to contract after the intravenous administration of 0.3 c.c. of posterior pituitary extract should be regarded as a grave sign and preparations for more active treatment of the uterine atony should be made without delay. It has been our experience that patients who fail to respond to the intravenous injections of posterior pituitary extracts usually require intrauterine packing to control post-partum bleeding.

Pitocin rather than pituitrin should be employed in patients with potential or actual toxemia of pregnancy to minimize the possibility of "pituitary shock," which may be caused by the pressor factor present in pituitrin.

CONCLUSIONS

1. Large intravenous doses (0.3 c.c.) of pituitrin, pitocin, and pitressin evoke similar oxytocic effects in the human post-partum uterus.

2. Equivalent dilutions of pitocin and pitressin, administered intravenously, produce equivalent oxytocic effects in the human post-partum uterus in spite of the wide variation in oxytocic values as assayed on the strips from the uterus of the virgin guinea pig.

3. Dilutions of pitocin and pitressin representing equivalent oxytocic activity by guinea pig assay method when given intravenously, are not equally effective in the human being.

4. The present methods of commercial assay do not give an index of the actual clinical oxytocic potency of pitressin.

5. There is no evidence that a tolerance develops in the human post-partum uterus following repeated intravenous injections of posterior pituitary preparations although there is usually a decreased response to repeated injections.

6. There is no inhibition of activity in the human post-partum uterus following injections of pituitrin or pitressin as has been described in laboratory animals.

7. The differences in the uterine responses of the post-partum patient and of the laboratory animal to posterior pituitary extracts are best explained as manifestations of a species difference.

8. A human oxytocic unit for posterior pituitary extracts has been defined.

The various preparations employed in this study were generously supplied by Parke, Davis and Co.

REFERENCES

(1) *Oliver, G., and Schafer, E. A.:* J. Physiol. **18:** 276, 1895. (2) *Dale, H. H.:* Ibid. **34:** 163, 1906. (3) *Blair-Bell, W., and Hicks, P.:* Brit. M. J. **1:** 777, 1909. (4) *Kamm, O., Aldrich, T. B., Grabe, L., Rowe, L. W., and Bugbee, E. P.:* J. Am. Chem. Soc. **50:** 573, 1928. (5) *Reynolds, S. R. M.:* Am. J. Physiol. **92:** 420, 1930. (6) *Reynolds, S. R. M., and Friedman, M. H.:* Ibid. **94:** 696, 1930. (7) *Rudolph, L., and Ivy, A. C.:* Am. J. Obst. & Gynec. **19:** 317, 1930. (8) *Blair-Bell, W., Datnow, M. M., and Jefficoate, T. N. A.:* J. Obst. & Gynaec. Brit. Emp. **40:** 541, 1933. (9) *Robson, J. M.:* Recent Advances in Sex and Reproductive Physiology, London, 1934, J. and A. Churchill. (10) *Kurzrok, R.:* Endocrines in Obstetrics and Gynecology, Baltimore, 1937, Williams and Wilkins Company. (11) *Morgan, T. N.:* J. Pharmacol. & Exper. Therap. **59:** 211, 1937. (12) *Robson, J. M., and Schild, H. O.:* J. Physiol. **92:** 1, 1938. (13) *Robson, J. M., and Schild, H. O.:* Ibid. **92:** 9, 1938. (14) *Danforth, D. N., and Ivy, A. C.:* Am. J. Obst. & Gynec. **37:** 194, 1939. (15) *Bourne, A. W., and Burn, J. H.:* Lancet **2:** 694, 1928. (16) *Adair, F. L., and Davis, M. E.:* Am. J. Obst. & Gynec. **27:** 383, 1934. (17) *Weinstein, G. L., and Friedman, M. H.:* Ibid. **29:** 93, 1935. (18) *Moir, C.:* Proc. Roy. Soc. Med. **28:** 1654, 1935. (19) *Van Dyke, H. B.:* The Physiology and Pharmacology of the Pituitary Body, Chicago, 1936, University of Chicago Press. (20) *Kamm, O.:* Personal Communication (1938).

THE DIAGNOSTIC SIGNIFICANCE OF THE ENDOMETRIAL GLANDS IN EARLY PREGNANCY

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THE diagnosis of pregnancy from curettage material has generally rested upon the presence of either decidua vera or chorionic villi in the specimen removed. In this paper attention is called to the importance of recognizing a characteristic pattern of increased glandular activity in the endometrium. This picture has been found consistently and early in the cases reported. Although this is a small group, it suggests that the unusual secretory activity described below may occasionally prove to be a reliable aid in the diagnosis of gestation. The significance of this finding lies in the fact that it may be the only diagnostic sign present. When biopsies were taken on seven of the patients, within six weeks from the last flow, neither the patient nor the doctor suspected pregnancy. In three of these seven specimens no decidua or villi were seen and the only indication of conception was found in the glands. In these three cases then, the diagnosis would have been missed if this pregnancy sign had not been recognized.

During the years 1935 to 1938, 1,500 endometrial biopsies have been prepared and examined in the Pathological Laboratory of the Massachusetts General Hospital.*

In this series of 1,500 biopsies, taken for a variety of gynecologic conditions, all phases of both normal and abnormal menstrual cycles have been observed. Eleven of the biopsies in this series, however, have

*The preparation of these slides was made possible through the interest and help of Dr. T. B. Mallory.

shown a certain similar and distinctly unusual pattern of secretion in the endometrial glands, and in 10 of these 11 cases an early pregnancy was confirmed by subsequent events. A description of the histology involved is presented first, followed by a summary of the 11 cases and finally, the single case in which pregnancy was not confirmed is presented in detail.

Most of the 1,500 biopsies were taken with a sharp-lipped retraction curette described by Meigs.* The tissue removed averages not more than 5 c. mm. in our hands and frequently less. Generally an attempt is made to scrape out tissue from the region of one or both cornua. The specimen is immediately fixed in Zenker's solution and paraffin sections are cut and stained with hematoxylin and eosin. We feel that such tissue, although small, gives a very satisfactory diagnosis of endometrial function. However, in the present series of 11 cases,

Fig. 1.—Case 10. Biopsy fifty days after onset of previous menses.

it is demonstrated that not infrequently such small pieces may be removed in early pregnancy without finding either decidual tissue or villi on microscopic study. It may be that the site of the biopsy was at a distance from implantation and that, in some of the early cases, the decidual response had not yet involved all of the functional endometrium. Possibly in other cases the superficial decidua-bearing layer was lost from the specimen in transfer. In any case, all eleven biopsies contained an adequate number of glands in the spongy layer showing unusual secretion to suggest a diagnosis of pregnancy.

Under low power, these glands are saw-toothed when cut longitudinally and star-shaped with many invaginations when cut across. In the spongy layer they lie crowded close together in early gestation and their general configuration is similar to that seen during the active luteal

*In press.

phase of the menstrual cycle. The lumina may contain cellular debris but not usually sufficient to cause distention of the gland walls which, more often, lie in contact. It is only under high power that the details of differentiative cytology can be seen. The epithelial cells lining the glands are swollen, larger and higher columnar in type than at any time in the normal menstrual cycle (Fig. 1). This forces them to bulge

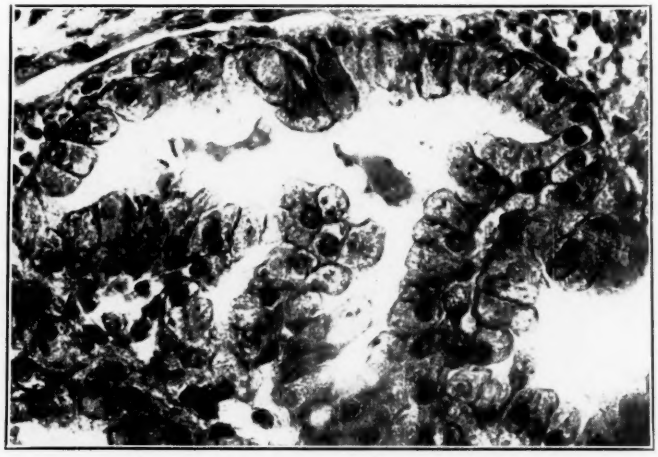

Fig. 2.—Case 4. Biopsy thirty days after onset of previous menses.

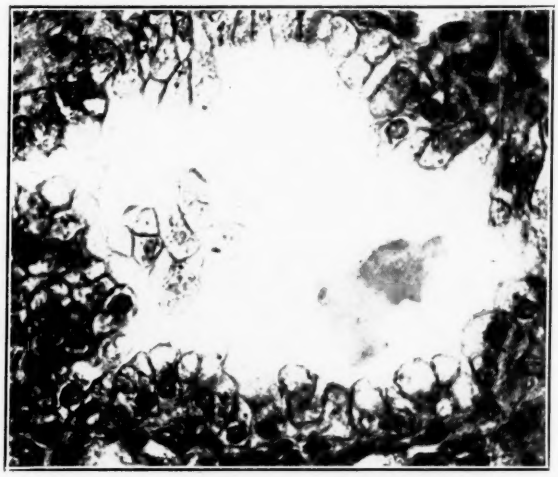

Fig. 3.—Case 7. Biopsy thirty-six days after onset of previous menses.

into the lumen like an exaggerated goblet cell (Fig. 2). They are filled with coarse, deep-staining granules, except at the luminal margin where these granules are absent and a fine reticular network can be made out (Fig. 3). Their free edge, ballooning out into the lumen, usually shows a clear-cut, sharp and distinct cell membrane (Fig. 4). The nuclei are round, light staining and near the basement membrane. There are no epithelial mitoses.

Table I summarizes the 11 cases out of 1,500 biopsies which showed this type of secretory activity. These cases are arranged chronologically from the earliest, taken twenty-five days after onset of the previous period to the latest removed sixty days after the menses. In the first eight, because of previous histories of irregular cycles, the presence of a pregnancy was not suspected at the time the biopsy was taken. The procedure was done in the clinic and the patients were allowed to go home. It is of interest that of these 8 cases where the pathological report gave

Fig. 4.—Case 5. Biopsy thirty-three days after onset of previous menses. Note the sharp distinct margin.

Fig. 5.—Case 8. Biopsy forty-two days after onset of previous menses. See case report.

the first positive evidence of conception and none but routine precautions were used, there have been 4 full-term babies and 3 others have successfully passed the first trimester. The remaining one, Case 8, is reported in detail below. In the last 3 cases, pregnancy was definitely suspected and the biopsy was done to substantiate the diagnosis with the patient in the hospital. In Case 9, the patient was bleeding and a diagnosis of incomplete miscarriage seemed probable at the time the specimen was removed. In Cases 10 and 11, biopsies were taken as an incidental pre-

TABLE I. SUMMARY OF CASES

CASE	PATH. NO.	INCREASED GLANDULAR ACTIVITY	DAYS AFTER LAST CATAMENIA	DECIDUA VERA	CHORIONIC VILLI	SUBSEQUENT PROOF OF PREGNANCY
1	37-1404	+	25	+	0	Baby
2	35-5096	+	27	+	0	Baby
3	38-4397	+	27	+	0	Aschheim-Zondek positive one week later
4	36-4927	+	30	0	0	Baby
5	38-5374	+	33	0	0	Aschheim-Zondek positive two weeks later
6	36-4927	+	34	0	0	Baby
7	38-4997	+	36	+	0	Aschheim-Zondek positive one week later
8	38-5359	+	42	0	0	Probable miscarriage. (See case report)
9	37-5547	+	45	0	+	Incomplete miscarriage. Dilatation and curettage
10	36-2614	+	50	0	0	Tubal pregnancy; salpingectomy
11	38-2189	+	60	+	0	Tubal pregnancy; salpingectomy

liminary to an operation for tubal pregnancy. It is clear then that in these cases endometrial biopsies taken early in pregnancy did not, as a rule, interfere with the course of gestation.

Decidua vera was encountered in only 5 slides and chorionic villi were found only once. In this group, then, the diagnostic significance of increased secretory activity is seen particularly in Cases 4, 5, 6, 8, and 10, where there was no other evidence of conception on a study of the microscopic section. In all the cases except Case 8 it was possible to corroborate this evidence either by a progression of the pregnancy, in Cases 1 to 7, or by operation in Cases 9 to 11.

CASE 8.—(Path. No. 38-5359.*) A 39-year-old white woman, married four and one-half years, under treatment for sterility. Two years previously a dilatation and curettage had been done for a probable incomplete miscarriage. There had been no other pregnancies. Her periods were usually regular, but four to six days early, and lasted six days; occasionally a month would be skipped. From March, 1938 through August, periods were regular. Her menses from September 27 to October 1 was two weeks late. It was then decided to do weekly endometrial biopsies until her next flow to determine if normal ovulation were occurring. The first specimen was taken October 4 and the sixth and last November 7, although the patient had started to have a little bleeding by November 2 which did not stop until November 14. During this twelve-day flow she was perfectly well and did not notice passing clots or tissue. Subsequently, she had a normal flow twenty-nine days afterwards.

*The author wishes to thank Dr. J. V. Meigs for his permission to use this case report.

In this case, 6 biopsies were taken approximately a week apart from the seventh to the forty-second day after onset of the September period. The last one showed an increased secretory activity in the glands suggesting early pregnancy (Fig. 5) but no decidua or villi. An Aschheim-Zondek test was not done.

It is possible to determine with reasonable accuracy how soon this characteristic glandular response occurs after ovulation from analysis of these six specimens. Biopsies 1, 2, and 3 showed normally developing proliferative endometrium. No. 4, on the twenty-eighth day of the cycle, was found to be in a typical early secretory phase, considered to be postovulatory. No. 5 showed normally active secretion and No. 6 taken on the forty-second day of the cycle but only two weeks after the first histologic evidence of ovulation, is seen to have the unusual pattern of gland activity described above.

It was concluded (A) that this patient occasionally ovulated late; in October, presumably around the twenty-fifth day of her cycle; (B) that the glandular response emphasized in this study occurs very early, within two weeks after fertilization (see also Table I, Cases 1, 2, and 3); and (C) that this patient had a complete miscarriage at home but failed to recognize the passage of the products of conception. It must be remembered, however, that the only evidence of gestation in this case is that the type of secretion in the endometrial glands is similar to that seen in the 10 other cases here reported of proved pregnancy.

DISCUSSION

In a previous report,[1] the unusually active appearance of secretion in the glands of the decidua vera was noted and contrasted with that seen during the height of the luteal phase of the normal cycle. In a later study of the duration of this response through pregnancy,[2] it was suggested that this increased activity might result from the added stimulus of the pregnancy urine (P. U.) hormone. Excretion of pregnancy urine hormone sufficient to give a positive Aschheim-Zondek test takes place consistently about five to six weeks from the last catamenia. There is evidence in at least 5 of the cases here reported (Cases 1, 2, 3, 4 and 8) that the characteristic glandular response to pregnancy is recognizable before the Aschheim-Zondek test usually becomes positive. It seems probable that increased secretion in the glands may reflect the earliest elaboration of this hormone and that this picture can be recognized before enough pregnancy urine substance is produced to spill over in detectable quantity in the urine.

SUMMARY AND CONCLUSIONS

1. Eleven cases are presented, showing an unusual picture of endometrial secretion.

2. Ten of these patients later proved to have been pregnant at the time the specimen was removed. The eleventh case is reported in detail.

3. Taking a biopsy by the method described did not inevitably interfere with the course of early gestation.

4. The characteristic glandular response here described represents an increase in function consistent with early pregnancy, and in these cases proved to be a reliable and valuable aid in the histologic diagnosis from endometrial biopsy specimens.

REFERENCES

(1) *Sturgis, S. H., and Meigs, J. V.:* Am. J. Surg. **33:** 369, 1936. (2) *Sturgis, S. H.:* Am. J. Obst. & Gynec. **35:** 752, 1938.

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SPECIFIC "TOXEMIA," ESSENTIAL HYPERTENSION, AND GLOMERULONEPHRITIS ASSOCIATED WITH PREGNANCY

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IT IS now generally felt that the term "toxemia" of pregnancy is general, vague, and inaccurate. W. W. Herrick[1] says, "Such a loosely used and inclusive term as toxemia of pregnancy can no longer be accepted as precise or specific. It should be subjected to critical analysis, perhaps dissected until there is nothing left." Irving[2] states "The term toxemia is now regarded as of poor descriptive value, since no toxin has been isolated in eclampsia, nor is the blood of eclamptic patients more poisonous than that of other pregnant women. The word toxemia has long been used to explain the manifestation of a disease, the nature of which we did not understand."

A great deal of confusion exists in the classifications of the toxemias. Obstetric textbooks disagree in their outlines of the types of toxemias. Stander[3] and his co-workers have reported their concept of a group of toxemic patients showing "low reserve kidney." Herrick[4] and his associates state, "The milder types of late toxemia, vaguely called low reserve kidney, recurrent toxemia, or nephritis, in their follow-up and necropsy manifestations, seem to resemble eclampsia and pre-eclampsia in that their frequent results are general vascular disease with hypertension rather than nephritis. The differences between the severe and milder types of nonnephritic late toxemias are of degree, not of kind." Kellogg[5] appeals for the universally accepted classification. He divides his patients into two large groups, namely, (a) those presenting evidence of disease independent of pregnancy and applies the Vollhard and Fahr classification of the nephropathies, adding to this pyelonephritis; and (b) those conditions specific to pregnancy, i.e., pre-eclampsia Grades 1 and 2; and eclampsia.

We use the following classification suggested by William Goldring (Lectures on Nephritis and Hypertension, Edward Brothers, Ann Arbor, Mich., 1937):

A. Specific toxemia of pregnancy.
   1. Without convulsions (pre-eclampsia)
   2. With convulsions (eclampsia)
B. Essential hypertension (pre-existing)
C. Glomerulonephritis (pre-existing)
D. Combinations of pre-existing essential hypertension or glomerulonephritis with superimposed specific toxemia.

During the past five years, we have attempted at Bellevue Hospital (1) to classify or group these patients; (2) to standardize their ob-

stetric care, if possible; (3) to determine the immediate effects on the mother and offspring; and (4) to determine the remote effects on the mother.

We believe that the treatment can be fairly uniform but must remain empirical, since the exact etiology is unknown. This treatment consists of (1) rest in bed, (2) sedatives (when indicated); (3) bowel hygiene, (4) in the presence of edema, the use of hypertonic solutions, 50 per cent sucrose and 10 per cent magnesium sulphate intravenously; salt poor and normal protein intake; and restriction of fluid intake not to exceed urinary output. When termination of pregnancy is considered, a vaginal examination is done to determine the state of the lower uterine segment and possible disproportion.

OCCURRENCE OF "TOXEMIA"

Dieckmann[6] says, "Approximately 8 per cent of the patients delivered in a maternity hospital had toxemia." He further quotes other observers, e.g., "The incidence of the toxemias of pregnancy for the Cornell University Clinic is 15.6 per cent and for the Johns Hopkins Clinic, 9.4 per cent as reported by Stander; Washington University Clinic 3.8 per cent according to Schwarz and Wegener; and 6.7 per cent for the University of Chicago Clinic. A conservative estimate of the number of patients with toxemia of pregnancy in the United States each year would be 100,000."

Our clinical study includes all patients from October, 1933, to October, 1938. During this five-year period there were 7,897 deliveries at Bellevue Hospital. Of these, 262 patients were observed through 272 pregnancies, complicated by the so-called toxemias. This is an incidence of 3.4 per cent.

All patients upon discharge were either referred to the Nephritis and Hypertension Clinic at the College or a similar special hospital follow-up clinic which has been in existence for three years.

AVERAGE AGE, PARITY, SIZE OF HEART AND RETINAS IN TOXEMIA

The following briefly analyzes some of the chief characteristics noted in each group (Table I):

A. Specific Toxemia.—The majority, 184 patients, were seen through 189 specific toxemic attacks. This is 69 per cent of the whole series.

1. Nonconvulsive: One hundred and sixty patients seen through 165 pregnancies were of the nonconvulsive type. The average age was 27 years. Primiparas prevailed and made up 64 per cent of this group. The hearts were chiefly not enlarged. Those showing enlargement were mainly due to rheumatic heart disease. The retinas frequently revealed hypertensive vessel changes (i.e., thinning, spasm or acute branching of arterioles, or A-V compression), whereas papilledema and areas of degeneration and hemorrhage were only occasionally present. Wagener[7] studied the arterioles of the retina in toxemia of pregnancy and found "that usually the first visible sign is a narrowing of the arterioles of the retina which may affect any or all of the branches of the central arteries. This narrowing is often accompanied or followed by irregular constrictions of the lumen of the arterioles, usually first or most marked in the smaller nasal branches, which may vary in degree and situation from day to day. Later, as the narrowing and constrictions become more fixed, individual cotton-wool patches and hemorrhagic areas may appear in the retina, and finally diffuse retinitis of the albuminuric type may develop."

TABLE I*

CLASSIFICATION NUMBER OF CASES		RECUR. NO.	AVERAGE AGE	PARITY		SIZE OF HEART		RETINAS					
				PRIMIP.	MULTIP.	NO. X-RAYED	E.H. NO.	NORMAL	H.V.C.	H.V.C. AND H.R.	H.V.C. AND P.E.	P.E.	H.V.C. AND H.R. AND P.E.
Specific "toxemia" 184	Non-convulsive 160	5	27	107	58	108	13	60	50	2	4	3	0
	Convulsive 24	0	27	12	12	12	0	6	5	0	4	0	1
Pre-existing essential hypertension 64	Uncomplicated 10	0	36	0	10	7	6	2	5	0	0	0	0
	Superimposed N.C.S.T. 51	5	35	4	52	36	29	4	25	6	2	1	6
	Superimposed C.S.T. 3	0	32	0	3	3	2	–	1	1	–	–	1
Glomerulonephritis 4	Uncomplicated 0	–	–	–	–	–	–	–	–	–	–	–	–
	Chronic diffuse with N.C.S.T. 3	0	23	1	2	3	1		2				1
	Acute diffuse 1	0	30	0	1	1	0		1				
Unclassified 10		0											
Total 262		10											

*N.C.S.T., Nonconvulsive specific toxemia; C.S.T., Convulsive specific toxemia; E.H., Enlarged heart; N., Normal; H.V.C., Hypertensive vessel changes; H.R., Hypertensive retinopathy (exudate and hemorrhage); P.E., Papilledema.

2. Convulsive: There were 24 specific toxemias with convulsions. Their average age was 27. Fifty per cent were primiparas, showing no cardiac enlargement. Their retinas showed hypertensive vessel changes with a greater tendency to papilledema.

B. Pre-existing Essential Hypertension.—Sixty-four women seen through 69 attacks began their pregnancies with pre-existing essential hypertension. They were 25 per cent of all the toxemias.

1. Uncomplicated: Only 10 or about 15 per cent remained uncomplicated. Analysis of the latter showed that their average age was 36 and each patient had had many pregnancies. Almost all those x-rayed had enlarged hearts. The retinas chiefly revealed hypertensive vessel changes.

2. Superimposed Nonconvulsive Toxemia: Fifty-one patients seen through 56 pregnancies developed superimposed nonconvulsive specific toxemia upon pre-existing essential hypertension. Their average age was 35 years. There were four young primiparas. The others had had many pregnancies; one was a para xvii. Eighty per cent of those x-rayed showed enlarged hearts. Their retinas showed more marked hypertensive vessel changes with a greater tendency to hemorrhage, areas of degeneration and papilledema.

3. Superimposed Convulsive Toxemia: Three patients developed convulsive specific toxemia superimposed on pre-existing essential hypertension. Their average age

was 32. They were multiparas, 2 showing enlarged hearts. Their retinas revealed marked hypertensive vessel changes, papilledema, hemorrhage, and areas of degeneration.

C. Glomerulonephritis.—In the entire series, there were only 4 patients with glomerulonephritis; none of these women remained uncomplicated. This limited incidence concurs with Young[8] who, in discussing chronic nephritis complicating pregnancy, said, "During a period of six years, when all our toxemias have been subjected to an intensive study, we have not found, among several hundred cases, more than four or perhaps five such cases."

1. Superimposed Specific Toxemia: Of this group, three patients with preexisting chronic diffuse glomerulonephritis developed superimposed specific toxemia. Their average age was 23 years. Two were multiparas and 1 was a primipara. Of the 2 multiparas, 1 had an enlarged heart. Both had hypertensive vessel changes and in addition, one showed hemorrhage and areas of degeneration in her retinas. The primiparous patient became pregnant about six months after an attack of acute diffuse glomerulonephritis. She had mild hypertension and albuminuria from the onset of pregnancy. She went to term and showed some increase in symptoms just before and during labor. Labor was medically induced and she spontaneously delivered a live child.

2. Acute Diffuse, Initial Attack: One patient at the onset of pregnancy developed acute diffuse glomerulonephritis following a sore throat. She was thirty years of age, a para ii with hematuria (by Addis Count), mild hypertension, proteinuria and generalized edema. Pregnancy was terminated by a therapeutic induction at three months.

D. Unclassified.—The 10 unclassified patients did not present sufficient criteria in early observation or because of no follow up for us to be able to place them in any known group.

LABOR, DELIVERY AND RESULTS TO MOTHER AND BABY (TABLE II)

A. Specific "Toxemia."—1. Nonconvulsive: Labor was chiefly spontaneous. There were only seven medical inductions and one bagging. We await spontaneous labor unless progression of the toxemia warrants induction. The latter is only attempted when the cervix is favorable. Ninety-four patients delivered spontaneously; 52 by operative means, such as forceps; and 18 by cesarean section. One woman died undelivered. There were 132 babies born alive; 42 were stillborn. Nine sets of twins were in this group; 4 mothers died.

2. Convulsive: Labor was chiefly spontaneous with only 2 medical inductions. Fifteen patients delivered of their own accord and 7 by forceps. The 2 sections will be analyzed later. There was 1 set of twins. Sixteen babies were born alive; 9 were stillborn. Four mothers died.

B. Pre-Existing Essential Hypertension.—1. Uncomplicated: Labor was chiefly spontaneous; 1 patient was induced by bagging. Three had cesarean sections and 7 delivered of their own accord. All mothers recovered and 4 babies were stillborn.

2. Superimposed Nonconvulsive Toxemia: Only 4 patients were induced medically. There were 11 cesarean sections; one of these was done post mortem. Forty-two delivered spontaneously and 3 by forceps. Twenty babies were stillborn and 1 mother died.

3. Superimposed Convulsive Toxemia: Two were delivered by elective cesarean section. One had spontaneous labor and was delivered by forceps. Two babies were born alive and 1 was stillborn. All mothers lived.

C. Glomerulonephritis.—1. Superimposed Specific Toxemia: The 2 multiparas had elective sections and although they recovered, their babies were stillborn.

OPERATIVE TERMINATION OF PREGNANCY AND LABOR (TABLE III)

Thirty-eight women had their pregnancies terminated by abdominal operation. One of these was a post-mortem cesarean. In 25, or 9 per cent, of the entire series,

TABLE II*

CLASSIFICATION NO. OF PATIENTS		RECUR. NO.	LABOR				DELIVERY			RESULTS		
				INDUCED						BABY		
			SPONT.	MEDICAL	BAG	NONE	SPONT.	OPER.	CESAREAN	ALIVE	DEAD	MOTHER DEATHS
Specific "toxemia" 184	Nonconvulsive 160	5	147	7	1	10	94	52	18	132	42	4
							1 Undelivered			9 Twins		
	Convulsive 24	0	22	2	–	–	15	7	2	16	9	4
										1 Twin		
Pre-existing essential hypertension 64	Uncomplicated 10	0	6	0	1	3	7	0	3	6	4	0
	Superimposed N.C.S.T. 51	5	42	4	0	10	42	3	11	36	20	1
	Superimposed C.S.T. 3	0	1	0	0	2	0	1	2	2	1	0
Glomerulonephritis 4	Uncomplicated 0											
	Chronic diffuse with N.C.S.T. 3	0	0	1	0	2	1	0	2	1	2	0
	Acute diffuse 1	0	0	0	0	1	D & C at 3 months			0	1	0
Unclassified 10		0	9	1	0	0	7	3	0	5	5	0
Total	262	10	227	15	2	28	166	67	38	198	84	9
							1 Undelivered					

*N.C.S.T., Nonconvulsive specific toxemia; C.S.T., Convulsive specific toxemia.

the prime motivating factor for the operation was the "toxemia." This is in contrast with the average cesarean rate of 2.3 per cent at Bellevue Hospital done for all other obstetric conditions.

Of the 20 operations in the specific toxemic group, 10 were primarily performed for reasons other than the toxemia. Of the remaining 10, giving an incidence of 6 per cent, 4 patients had severe early toxemia and 6 had impending convulsions. The two listed under the convulsive group were done prior to the onset of this complication. It is our policy to treat the convulsive patients conservatively. A woman with abruptio placentae had a hysterectomy. There were 2 tubal sterilizations. There was one maternal death. This patient received gum acacia to combat shock. At this time, other deaths and severe reactions to gum acacia were noted on the service.[9]

Of the patients with pre-existing essential hypertension, 13, or 18 per cent, had their pregnancies terminated by the abdominal route because of toxemia. Nine had repeated toxemias. Two had severe attacks in the second trimester of pregnancy and two had impending convulsions. Ten were sterilized and one had a hysterectomy.

The 2 hysterotomies done in the nephritic group were indicated because of severe superimposed specific toxemia. Both had tubal sterilization. Their clinical course fitted into the picture described by Herrick and Tillman[10] who said, "With repeated

TABLE III. TERMINATION OF PREGNANCY BY ABDOMINAL OPERATION*

CLASSIF. AND NO.	NO. OF OPER.	OTHER THAN TOX.		COR. NO.	% OPER. FOR TOX.	TOXEMIA INDICATIONS			TYPE OF OPER.		STERILIZATION	MAT. DEATHS
		PELVES, ETC.	ABRUPTIO PLACENTAE			SEVERE EARLY	IMPENDING CONVUL.	REPEATED TOX.	SECTION OR HYSTEROTOMY	HYSTEREC-TOMY		
N.C.S.T. 165	18	8	2	8	6	4	4	0	17	1	2	1
C.S.T. 24	2	Both done as non-convulsive		2	0	-	2	-	2	-	-	-
Essen. hyper. 69	15	-	2	13	18	2	2	9	14	1	10	-
Glom. neph. S.T. 3	2	-	-	2	66	-	2	-	2	-	2	-
Total tox. 272	37	8	4	25	9	6	10	9	35	2	14	1

*Cesarean rate for all obstetric indications was 2.3 per cent; N.C.S.T., Nonconvulsive specific toxemia; C.S.T., Convulsive specific toxemia.

pregnancies, the renal breakdown appears earlier in pregnancy and is usually more serious and the result is less likely to be a living child. In a woman with nephritis, repeated pregnancy seems to encroach further on the factor of safety of the kidney and should be avoided.''

Twenty-eight per cent of the remaining patients were delivered by forceps. This was done for prematurity, and in order to shorten the second stage, since toxemia tends to increase during this part of labor.

RECURRENCE OF TOXEMIA

A. Specific Toxemia.—This symptom complex shows a tendency to recur in subsequent pregnancies. Some patients ultimately remain with permanent hypertension after one of these attacks (Table V). While the period of follow-up in this study is not sufficiently long to answer the question, our impressions confirm the observations of others[11] that more than 50 per cent of toxemic women become permanently hypertensive. Many important questions arise, i.e., (1) What factors during an attack of specific toxemia will decide its recurrence or development of a permanent hypertensive state? Is it the clinical course of the disease in relation to (a) severity, (b) duration, (c) the period of gestation when symptoms began, or (d) is it the time required for the symptoms of the last attack to disappear, or (e) are there

TABLE IV. RECURRENCE OF SPECIFIC ''TOXEMIA''

PARA	NO. OF CASES	TOXEMIA RECURRED NO.	PREVIOUS NORMAL PREGNANCIES NO.
ii	25	20	5
iii	11	3	8
iv	7	3	4
Total	43	26	17
Per cent		60	40

combinations of these factors? (2) Is it some underlying glandular or vascular defect with which these women are born or develop later on? In order to answer some of these questions, it is necessary to follow patients from an initial attack of specific toxemia between and through subsequent pregnancies and also to the necropsy table.

We have accumulated enough evidence to show that specific toxemia recurs. To date, it is premature for us to analyze the primiparas in this series during and between subsequent pregnancies. However, an analysis of those who had specific toxemia when they first presented themselves as para ii, iii, or iv shows that 60 per cent had at least one previous attack (Table IV).

B. Pre-Existing Essential Hypertension.—It was pointed out that multiparity is the rule in this group. About 75 per cent of these patients had at least one, more often many attacks of specific toxemia in previous pregnancies. Many of the remaining 25 per cent were delivered at home, having had no prenatal or interpregnancy supervision.

We selected 10 patients as a few of the group who were seen in their last pregnancy with pre-existing essential hypertension and specific toxemia (Table V). They

TABLE V*

NAME	AGE L.P.	PARA i	ii	iii	iv	v	vi	
C. B.	26	S.T.	ESS. S.T.					Essential hypertension
E. M.	25	S.T.	S.T.	ESS. S.T.				Essential hypertension
M. S.	36	O	O	S.T.	ESS. S.T.			Essential hypertension
H. S.	35	O	O	S.T.	S.T.	ESS. S.T.		Essential hypertension
F. C.	34	O	O	O	S.T.	ESS. S.T.		Essential hypertension
L. C.	30	O	O	O	O	C.S.T.	ESS. S.T.	Essential hypertension
A. W.	42	S.T.	O	O	S.T.	S.T.	ESS. S.T.	Essential hypertension
M. K.	37	ESS. S.T.	ESS. S.T.	ESS. S.T.	ESS. S.T.	ESS. S.T. H.F.		Hypertensive H.D. with failure
E. S.	42	O	O	O	S.T.	S.T.	ESS. S.T. H.F.	Hypertensive H.D. with failure
C. F.	33	O	O	O	S.T.	ESS. S.H. S.T.	ESS. S.H. S.T. S.H.	

*ESS., Pre-existing essential hypertension; C.S.T., Convulsive specific toxemia; S.H., Subarachnoid hemorrhage; O., Normal pregnancy; H.F., Heart failure; S.T., Specific toxemia; L.P., Last Pregnancy; H.D., Heart Disease.

had attacks of specific toxemia in their previous pregnancies and entered their last one with permanent hypertension. They show some interesting facts, i.e., (1) One attack of specific toxemia may terminate in essential hypertension. (2) Attacks need not appear in successive pregnancies for the latter to occur. (3) It is interesting to note that 2 of these women developed marked congestive heart failure as a result of hypertensive heart disease. (4) Six out of these 10 women had permanent hypertension at the age of 35 or younger. There were 2 around 25 years of age. It has become evident in the past few years that the cardiovasculorenal

field is intimately connected with the toxemias of pregnancy in the active part of the disease, in subsequent pregnancy and in the intervals between pregnancies. Herrick and Tillman[10] made an extensive follow-up study of 594 posttoxemic patients over a period of from one to twenty-two years or an average time of 5.6 years. Ninety women had died. Of these, 80 per cent were from causes within the cardiovasculorenal field. Irving[2] states, "There is considerable evidence that the disease (eclampsia) is vascular in nature and may best be explained on the basis of arteriolar spasm."

C. Pre-Existing Glomerulonephritis.—The 2 multiparous patients of this group had attacks of superimposed specific toxemias in all their previous pregnancies.

FETAL AND MATERNAL MORTALITY

A. Fetal.—Many factors contribute to the high fetal mortality rate. They are (1) prematurity, spontaneous or induced by the attendant, who is forced to terminate a pregnancy in order to lessen the immediate or remote hazards to the mother. (2) Immaturity, very often the fetus of a toxemic mother is smaller than that of a normal pregnancy of a like gestational period. (3) Intrauterine deaths, which often cause sudden improvement of the maternal status. The causes of these pregnancy deaths have theoretically been explained on the basis of possible placental changes; but as yet, no irrefutable evidence has been given of this phenomenon.

In this series, we did not differentiate nonviable from viable deaths but considered all fetuses dead if they did not live through the neonatal period.

The fetal death rate for all patients exclusive of toxemia during the period covered by this report was 3.6 per cent. In the toxemias, this rate was 30.8 per cent (Table VI).

TABLE VI. FETAL AND MATERNAL MORTALITY

FIVE YEARS ENDING OCTOBER, 1938	NO.	FETAL DEATHS		MATERNAL DEATHS	
		NO.	%	NO.	%
Nontoxemic pregnancies	7625	281	3.6	25	0.32
"Toxemias"	272	84	30.8	9	2.8

B. Maternal.—The 3 outstanding causes of maternal mortality in the pregnant, parturient and post-partum periods are hemorrhage, sepsis, and the toxemias.

The uncorrected mortality rate among the toxemic patients was 2.8 per cent, compared with 0.32 for all other obstetric patients during this period.

SUMMARY

1. A workable classification for the so-called toxemias of pregnancy has been presented.

2. The dangers of toxemia are immediate and remote. If the condition progresses notwithstanding conservative medical treatment, pregnancy should be terminated.

3. The frequency with which essential hypertension follows toxemia of pregnancy has caused growing concern. While toxemia may actually induce persistent hypertension, it is possible that the pregnancy merely makes evident a latent hypertensive state. It is incumbent upon obstetricians to recognize that such a state may supervene. Therefore, a decision must be arrived at cautiously when judging the advisability of future pregnancies following one complicated by toxemia.

4. The imminent and future dangers of a pregnancy complicated by pre-existing essential hypertension should be discussed with the family. If the patient has living children, that pregnancy should be terminated and future ones avoided. Not infrequently, the method of choice is

hysterotomy with tubal sterilization. Fifteen out of 69 such pregnancies were terminated by abdominal operation. Ten women had tubal sterilizations.

5. Pre-existing glomerulonephritis is rare during pregnancy. It usually becomes complicated by specific toxemia.

6. The second stage of labor should be shortened by simple forceps delivery in order to prevent cerebral injuries in premature births and to forestall progression of the toxemic state.

7. The maternal mortality rate is high, the uncorrected rate in our series was 2.8 per cent.

8. There was a total fetal mortality rate of 30.8 per cent.

REFERENCES

(1) *Herrick:* Tenth Annual Graduate Fortnight, New York City, 1937. (2) *Irving:* Am. J. Obst. & Gynec. **31:** 466, 1936. (3) *Stander and Kuder:* Ibid. **35:** 1, 1938. (4) *Herrick, Tillman, and Gebene:* Ibid. **31:** 832, 1936. (5) *Kellogg:* Am. J. Surg. **35:** 300, 1937. (6) *Dieckmann:* Am. J. Obst. & Gynec. **29:** 472, 1935. (7) *Wagener:* J. A. M. A. **101:** 1380, 1933. (8) *Young:* J. Obst. & Gynaec. Brit. Emp. **39:** No. 2, 1932. (9) *Studdiford:* Surg. Gynec. Obst. **64:** 772, 1937. (10) *Herrick and Tillman:* Arch. Int. Med. **55:** 643, 1935. (11) *Corwin and Herrick:* Am. J. Obst. & Gynec. **14:** 783, 1927.

CONGESTIVE HEART FAILURE IN PREGNANCY

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SINCE the publication of Sir James Mackenzie's[1] book, *Heart Disease and Pregnancy*, a growing interest has developed in this subject. A large number of such patients are observed annually at the Woman's Clinic of the New York Hospital. The nature of their heart disease and the results of its management in a special cardiac clinic were reported in 1937 by Stander and Kuder.[2] While most of them experienced no cardiac difficulty during pregnancy, the maternal mortality of the group was twice as great as the general maternity mortality of the clinic and accounted for 10 per cent of the obstetric deaths. Since the report by Stander and Kuder, many more cardiac patients have been observed at the Woman's Clinic of the New York Hospital, and considerable information has accumulated concerning them. For the present report, information relating to those patients who developed cardiac failure associated with pregnancy has been analyzed.

RESULTS

Among 22,837 obstetric patients delivered in the last six and a half years, there were 620 with organic heart disease. Only 26 of these patients developed physical signs of congestion of the lungs or abdominal viscera associated with pregnancy. Heart failure thus occurred in less than 0.1 per cent of all pregnant patients and in approximately 4 per cent of all cardiac patients.

All degrees of congestive heart failure were found among the 26 patients studied, and details relating to its manifestations and course are recorded in Table I. The month of pregnancy at which each patient was first seen in heart failure is listed in column two, and when more than one attack occurred the month of each attack of failure is shown. The degree of pulmonary and hepatic congestion and edema has been recorded in columns three, four, and five on the arbitrary basis of + to ++++, acute pulmonary edema being considered ++++ pulmonary congestion. The type of delivery is also shown in this table. Forceps deliveries are included under spontaneous deliveries. The last column gives the latest follow-up of the case, using the functional classification 1, 2A, 2B, and 3 of the American Heart Association.

When the findings were tabulated in this way they fell into four distinct groups.

TABLE I. MANIFESTATIONS AND COURSE OF HEART FAILURE*

CASE	MONTH	MANIFESTATIONS			DELIVERY	REMARKS
		LUNG	LIVER	EDEMA		
			Group I			
1	3	+	+	+	Section	2A, 18 mo. later
2	4	+	0	+	Section at 5 mo.	Not seen since discharge
3	5	+	0	0	Spontaneous	2A, 7 yr. later; pregnant again
4	5	++	0	+	Section	2A, 4 yr. later
5	5	+	0	0	Section	2A, 6 mo. later
6	6	++	0	0	Section	2A, 6 yr. later
7	7	++	0	0	Section	2A on discharge
8	8	+	0	+	Spontaneous	2A, 4 mo. later
9	8	+	0	0	Spontaneous	AF and failure 2 yr. later; died 5 yr. later
10	PP	+	0	0	Spontaneous	Bronchitis; 2A, 2 mo. later
			Group II			
11	10	+++	0	0	Spontaneous	2A, 1 mo. later
12	10	++++	0	0	Spontaneous	2A, 8 mo. later
13	10	++++	0	+	Spontaneous	4 subsequent attacks of cardiac failure; death 5th attack 2 yr. later
14	PP	++++	0	0	Section	2A, 15 mo. later; alive 6 yr. later
			Group III			
15	4	++	0	+		
	10	++	0	+		
	1 PP	+++	+	+	Spontaneous	Mild failure 2 mo. PP
16	5	++++	+	++	No	Died undelivered 2 hr. after admission
17	5	+++	+	0		
	8	++++	0	++	No	Died undelivered 8th mo.
18	5	+++	0	+		
	PP	++++	0	0	Section	Died 1 day PP
19	6	+++	0	0		
	7	++++	0	0	Section	2A, 14 mo. later
20	6	+++	0	+		
	8	+++	0	0	Section	2A, 8 mo. later
21	7	+++	0	0	Spontaneous	2A, 2 mo. later
22	8	+++	0	0	Section	2A at discharge
23	9	+++	0	0	Section	2A, 2 mo. later
			Group IV			
24	4	+	+++	+++	Section at 5 mo.	Died 11 days PO
25	6	+++	++	+++	Section	2B, 1 yr. later
26	6	++	+++	+	Section	Mild failure 2 yr. later; 2A, 4 yr. later

*PP, post partum.
PO, postoperative.

Group I.—There were 10 patients who had mild failure with a few persistent râles at the lung bases but little or no liver enlargement or edema. These signs appeared in different patients in almost every month of pregnancy and in the early puerperium, and all patients responded well to treatment.

Group II.—Four patients remained compensated throughout pregnancy but developed a marked degree of failure with delivery.

Group III.—There were 9 patients who developed a severe degree of heart failure before delivery, with signs of congestion principally in the lungs. Except for one who died in pulmonary edema two hours after admission to the hospital, all of them improved under treatment. Three of them (Cases 21, 22, 23) remained compensated during the remainder of the period observed. There were 5 in whom heart failure reappeared.

Group IV.—There were only 3 of the 26 patients in whom massive edema and marked liver enlargement developed in addition to the pulmonary congestion. All of them regained compensation and two were allowed to go to term.

NATURE OF THE HEART DISEASE

The cardiac findings in these patients have been analyzed in detail, so that they could be compared with the manifestations of heart failure by which these cases were grouped. The findings are recorded in Table II.

The type of valve lesion, previous history, and other cardiac findings listed in this table indicate a moderate degree of cardiac damage and are approximately the same for the patients who were classified as Groups I, II, and III on the basis of the nature of their heart failure. The patients in Group IV, on the contrary, all had advanced heart disease with large hearts and auricular fibrillation.

The factors which had an important bearing on the precipitation of heart failure in these pregnant cardiac patients as listed in Table II were many and need further explanation. Four patients were markedly overweight. In 6, coryza, sore throat, or hoarseness indicated that a respiratory infection immediately preceded the development of congestion of the lungs. Four patients had a slight degree of anemia, and three a severe anemia. One of these (Patient 20), who was admitted in heart failure during the fifth month of pregnancy, had a hemoglobin of 39 per cent, and a red blood cell count of 2 million. With liver and iron therapy and four small (125 to 150 c.c.) transfusions, her blood was restored to normal level before term. Another (Patient 17) was admitted in her second attack of heart failure during the eighth month of her pregnancy. She was in pulmonary edema, and a phlebotomy of 500 c.c. was necessary for relief. The following day her red blood cells numbered 2,900,000 and her hemoglobin 46 per cent. Six days later, when she had regained compensation, she was given a 100 c.c. transfusion. When a second transfusion was just beginning on the following day she developed a fatal attack of pulmonary edema.

In six patients there was some evidence of active rheumatism. The electrocardiograms of two showed questionable first degree heart block (PR 0.21). A third developed an acutely inflamed joint during her convalescence from heart failure. Another recovered from a typical attack of rheumatic fever just before pregnancy and two had pains without joint deformity during pregnancy. But these manifestations were not sufficient to indicate that an active rheumatic carditis precipitated heart failure in any instance.

Five patients had cardiac arrhythmias associated with heart failure. Two had probably been fibrillating for a long time. Patient 24 had been observed in the medical cardiac clinic for several years and her attack of heart failure followed the onset of auricular fibrillation. Patient 20 developed auricular fibrillation after recovery from decompensation, but her heart failure was not increased by it. The rhythm was reverted to normal by quinidine administration and continued so during the remainder of the observation. Patient 19 had three attacks of paroxysmal auricular tachycardia shortly after she was admitted in failure. There was no history to indicate that the failure was precipitated by such an attack and the passive congestion was not increased by the paroxysms observed.

TABLE II. NATURE OF THE HEART DISEASE AND COMPLICATIONS

CASE	VALVE LESION	PREVIOUS HEART FAILURE	PREVIOUS CARDIAC SYMPTOMS	RHYTHM	ELECTRO-CARDIOGRAM	CARDIAC ENLARGEMENT	REMARKS
				Group I			
1	M. S.	Yes	Yes	Normal	RAD	None	
2	M. S.	No	No	Normal	RAD	Moderate	
3	M. S.	No	Yes	Normal	Normal	Moderate	Rheumatic fever immediately before pregnancy
4	M. S.	No	No	Normal	Normal	Slight	
5	M. S., A. I.	No	Yes	Normal	None	Moderate	URI; joint pains without deformity
6	M. S.	Yes	No	Normal	Normal	Slight	Obese
7	M. S.	No	No	Normal	PR 0.21	Moderate	Hg 65%
8	M. S., A. I.	No	No	Normal	Normal	Slight	R.B.C. 3.2 mil.; Hg 60%
9	M. S., A. I.	No	Yes	Normal	RAD; $P_{1, 2, 3}$ split	Marked	Hg 60%
10	M. S.	No	Yes	Normal	Normal	Slight	
				Group II			
11	M. S.	No	No	Normal	None	No x-ray	URI; obese; R.B.C. 4.25 mil.; Hg 60%
12	M. S., A. I.	No	No	Normal	Normal	Marked	
13	M. S.	Yes	Yes	Normal	RAD	Slight	R.B.C. 3.8 mil.; Hg 40%
14	M. S.	No	No	Normal	Normal	None	URI
				Group III			
15	M. S.	Yes	Yes	Normal	RAD	Moderate	Obese
16	Not determined	No	No	Normal	None	No x-ray	
17	M. S., A. I., A. S.	No	No	Normal	Normal	None	URI; R.B.C. 2.9 mil.; Hg 46%
18	M. S.	No	Yes	Normal	Normal	Moderate	
19	M. S.	Yes	Yes	Normal	RAD; PR 0.21	None	Paroxysmal auricular tachycardia
20	M. S.	No	No	Normal	Normal	None	Transitory auricular fibrillation; R.B.C. 2 mil.; Hg 39%
21	M. S.	No	Yes	Normal	RAD	Slight	URI; inflamed joint during convalescence from heart failure
22	M. S.	No	Yes	Normal	Normal	None	Obese
23	M. S.	Yes	No	Normal	Normal	Moderate	URI; joint pains without deformity
				Group IV			
24	M. S.	No	Yes	Aur. Fib.	RAD; IVHB	Marked	Relative tricuspid insufficiency
25	M. S., A. I.	Yes	Yes	Aur. Fib.	LAD	Marked	
26	M. S.	Yes	Yes	Aur. Fib.	LAD	Marked	

The valve lesions are shown in the first column. M. S. refers to mitral stenosis, A. I. to aortic insufficiency, and A. S. to aortic stenosis. History of previous heart failure and of symptoms indicating an impaired cardiac reserve just before pregnancy are listed in columns three and four. The heart rhythm is shown in column five, the electrocardiographic findings in column six. RAD and LAD refer to right and left axis deviation, and when the conduction was delayed, the PR time is recorded. IVHB indicates an intraventricular heart block. The heart size by x-ray is shown in column seven. Extracardiac conditions which had a bearing on the development of heart failure are listed in column eight. URI indicates an upper respiratory tract infection, and in anemic patients the red blood cell count and hemoglobin are recorded.

DISCUSSION

When a woman with heart disease becomes pregnant, a number of important problems relative to her management arise. The first of these is to determine whether the cardiac status will permit her to proceed safely with the pregnancy. This decision as well as the management of the patient throughout the remainder of her pregnancy will naturally depend upon an understanding of the patient's probable course. It is important to know how likely heart failure is to appear, what factors are responsible for its development, how it will first be manifest, and what course it will probably take. These questions are best answered by studying those patients who developed heart failure during pregnancy.

Only a small number of patients develop heart failure during pregnancy.

In our series, it occurred only 26 times in 620 pregnancies of patients with organic heart disease, an incidence of 4 per cent. This figure is considerably lower than any previously reported. Jensen,[3] from a review of the work of Carr and Hamilton,[4] Jaschke,[5] Fromme,[6] and Laennec,[7] concluded that about 20 per cent of women with heart disease develop failure during pregnancy. Bramwell and Longson[8] had 36 instances of failure among 350 patients with heart disease. The much lower incidence which we have found depends upon two facts. First, we selected only those patients showing physical signs of passive congestion. Although there were as many other patients who, because of the severity of their symptoms, were hospitalized early, given digitalis, or delivered by cesarean section, these were the only ones who showed definite objective evidence of heart failure. Second, the 620 patients were followed as closely as possible throughout their pregnancies in a special cardiac clinic and there can be no doubt that heart failure was prevented many times by careful management.

CAUSE OF HEART FAILURE

Granted then that heart failure will develop in only a very small percentage of cases, the question arises: Why do these few patients develop it? A survey of the data in Table II indicates two causes. They are the degree of heart disease and the presence of those extracardiac factors which favor the development of heart failure in patients whose heart disease alone might not necessarily have caused trouble. This latter factor explains the appearance of heart failure in patients with only mildly damaged hearts and the lack of parallel observed above between the severity of heart disease and the degree of heart failure.

Only about half of our patients had sufficient evidence of cardiac damage to lead us to expect that their hearts might fail during pregnancy. There are reports of heart failures occurring in women whose hearts were perfectly normal before pregnancy but all the more reliable recent work indicates that heart failure develops only in those with well-recognized organic heart disease. With few exceptions they have mitral stenosis of the type seen after rheumatic fever, and the involvement of other valves is not usually important. Our cases were all of this type. The number of previous pregnancies appears to have no bearing on the development of heart failure but the factor of age

is as important in pregnancy as at any time. Of 1,633 patients with rheumatic heart disease studied by DeGraff and Lingg,[9] the average age for the development of cardiac insufficiency was 28 years, for the development of heart failure, 30 years, and the average age at death was 33 years. Our figures show the same approximate age grouping, since 16 of our 26 patients who developed heart failure were 30 or more years old. As Hamilton[10] has previously emphasized, age is one of the most important guides to prognosis of heart disease in pregnancy.

The functional classification of the American Heart Association which Pardee[11] first applied to the management of heart disease in pregnancy has been invaluable in the management of our cases. When the symptoms described by the patients did not appear compatible with the findings, exercise tests, especially stair climbing, were used. Among the patients who developed heart failure during pregnancy, 8 had previously had heart failure, and there were 14 who had symptoms in the months just prior to pregnancy, that indicated a diminished cardiac reserve. A large percentage of our patients showed enlargement of the heart by x-ray and even in those in whom the heart was of normal size, its configuration was distinctly abnormal. The electrocardiogram showed a right axis deviation in 8 of the cases, and 3 patients had auricular fibrillation.

A consideration of the data listed in Table II shows that the evidence of cardiac damage just discussed was not marked in about half of the patients who developed heart failure. In these cases there was usually an important extracardiac factor to account for it. In his book, *Failure of the Circulation*, Harrison[12] has listed the following as precipitating causes of heart failure: infection, exertion, cough, pregnancy, anemia, tachycardia, obesity, change of rhythm, emotional upsets, and prolonged mental strain. Almost all of these were found to be associated with heart failure in our series in addition to the pregnancy. Some of them seem to be considerably more important than others. Anemia was frequent and in two instances added considerably to the gravity of the situation. The factor of overexertion, which Hamilton[10] considers an important precipitating cause of heart failure during pregnancy, was not conclusively found to be such in any of our cases. It was, however, an important cause of the recurrence of heart failure. Upper respiratory tract infections were the most frequent and serious complications. Just how they affected the heart is not clear, for there was no definite evidence of any myocardial change in the patients with colds and bronchitis. This was also true of the patients who had rheumatic phenomena, for none of these showed sufficient electrocardiographic abnormality to indicate an active rheumatic myocarditis. One can only conclude that if rheumatic and respiratory tract infections cause myocardial change in pregnant women with heart disease, our present methods are inadequate to detect them. There seems to be little doubt, however, that in pregnant women, with relatively little evidence of cardiac damage, these infections have an important role in the development of congestive heart failure.

MANIFESTATIONS OF HEART FAILURE

In 1933 Carr and Hamilton[4] reported that the incidence of heart failure increased progressively from the third to the ninth lunar month of pregnancy, after which it decreased progressively. Within the last year Cohen and Thomson,[13] working in Hamilton's department, have shown that those circulatory factors associated with the increased cardiac burden of pregnancy follow a curve which parallels that formed by figures of Carr and Hamilton. Contrary to these reports, Jensen,[3] who analyzed a much larger series of cases, was unable to find any particular time in pregnancy when heart failure was most likely to appear. The number of patients in our series is obviously too small to support or refute either of these findings. Our cases do show clearly, however, that there is no time after the second month of pregnancy when heart failure does not occur. Since the factor of cardiac work is not alone responsible for the development of heart failure during pregnancy, this is to be expected. In patients who have had heart failure before term and in those who have not, acute and severe decompensation is not uncommon within the first twenty-four hours after delivery or cesarean section. This fact, which has been well known for some time, has never been satisfactorily explained.

The data in Table I indicate that congestion of the lungs is by far the most frequent and important sign of heart failure during pregnancy. Even though peripheral edema is frequently seen in normal pregnancy, it was seldom present in the patients with heart failure and became marked only in those with auricular fibrillation. The latter likewise were the only ones to develop any significant degree of hepatic engorgement. This predominance of congestion of the lungs probably means that heart failure occurs in a more fulminating form during pregnancy than at other times. Moreover it is precipitated by the pregnancy before it would otherwise occur in the normal course of rheumatic heart disease. Congestion of the lungs is an early manifestation of heart failure, while edema and liver enlargement occur late. Pulmonary congestion was associated with paroxysmal nocturnal dyspnea in two patients (Patients 2 and 22) and with hemoptysis in five (Patients 2, 5, 19, 20, 21). It frequently became marked without other manifestations of passive congestion and progressed to acute pulmonary edema in seven patients. Acute pulmonary edema was the immediate cause of death in three of the four fatal cases.

COURSE OF HEART FAILURE

The patients we have studied have taken several courses. Only four of them died. Those who showed mild manifestations of failure passed through the remainder of pregnancy without complications. There were four patients, however, who developed severe heart failure at term, even though they had had no signs of failure during pregnancy. Five of the nine patients who had relatively severe pulmonary congestion in early pregnancy developed a recurrence of it. Most of these relapses probably would not have occurred if the patient's activity

had been restricted more. Four of the 5 patients in whom a recurrence of heart failure developed had been allowed out of bed, and three of them had been allowed to leave the hospital. Moreover, two patients who had auricular fibrillation and advanced heart disease remained compensated in bed and were delivered by cesarean section.

Because of these experiences, we are convinced that patients who have once had congestive heart failure can almost always be maintained in a state of good compensation for several months even though the burden on the heart increases progressively as the pregnancy advances. There is good reason to believe that the work of the heart is decreased during the last few weeks of pregnancy. For these reasons, the interruption of pregnancy before term for congestive heart failure is indicated only in rare instances.

SUMMARY AND CONCLUSIONS

Among 22,837 patients with full-term and premature deliveries observed during the last six and a half years in the Woman's Clinic of the New York Hospital, 620 cases were complicated by organic heart disease. A study of those patients in this group who developed heart failure yielded the following information:

1. Congestive heart failure occurred in 4 per cent of the pregnancies complicated by organic heart disease. The mortality of those who developed congestive heart failure was 15 per cent.

2. The development of heart failure depended upon two factors: (a) severity of cardiac damage, and (b) extracardiac causes responsible for the precipitation of heart failure in women with slightly or moderately damaged hearts. These extracardiac causes were associated with the heart failure in approximately half of the cases. They included nearly all of the recognized precipitating causes of heart failure, but upper respiratory tract infections and anemia were the most important.

3. Congestion of the lungs usually was the only manifestation of heart failure in these patients. It was associated with hemoptysis in 20 per cent of them and progressed to acute pulmonary edema in 25 per cent. Acute pulmonary edema was the cause of death in 3 of the 4 fatal cases. Massive peripheral edema and marked liver enlargement occurred only in those with auricular fibrillation.

4. Heart failure developed during each of the last eight months of pregnancy and was not uncommonly first seen within the first twenty-four hours after delivery. It responded well to treatment but reappeared in about one-fourth of the patients. These relapses occurred only when the initial attack of failure was severe and would probably have been avoided in most cases if the patients had been more restricted in their activity.

5. With proper management almost all patients who have heart failure will improve and can be maintained in good compensation for several months, even though the burden on the heart increases pro-

gressively as the pregnancy advances. After the fourth month, the interruption of pregnancy for congestive heart failure is seldom indicated.

REFERENCES

(1) *Mackenzie, Sir James:* Heart Disease and Pregnancy, London, 1921, Oxford Medical Publications. (2) *Stander, H. J., and Kuder, K.:* J. A. M. A. **108**: 2092, 1937. (3) *Jensen, Julius:* The Heart in Pregnancy, St. Louis, 1938, The C. V. Mosby Company. (4) *Carr, F. B., and Hamilton, B. E.:* Am. J. Obst. & Gynec. **26**: 824, 1933. (5) *Jaschke:* Quoted by Jensen. (6) *Fromme:* Quoted by Jensen. (7) *Laennec:* Quoted by Jensen. (8) *Bramwell, C., and Longson, E. A.:* Heart Disease and Pregnancy, London, 1938, Oxford University Press. (9) *DeGraff, A. C., and Lingg, C.:* Am. Heart J. **10**: 459, 1935. (10) *Hamilton, B. E.:* J. A. M. A. **91**: 1942, 1928. (11) *Pardee, H. E. B.:* Am. J. Obst. & Gynec. **17**: 255, 1929. (12) *Harrison, T. R.:* Failure of the Circulation, Baltimore, 1935, Williams and Wilkins. (13) *Cohen, M. E., and Thomson, K. J.:* J. A. M. A. **112**: 1556, 1939.

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THE MANAGEMENT OF PLACENTA PREVIA

With an Analysis of 260 Consecutive Cases*

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IN THE ten-year period ending Jan. 1, 1939, 260 cases of placenta previa occurred in the 34,879 obstetric admissions to Charity Hospital of Louisiana at New Orleans, an incidence of 1:134. The maternal mortality in this series was 20, 7.6 per cent, and the gross fetal mortality 84, 32.3 per cent. Since the maternal deaths from placenta previa accounted for 8.3 per cent of the entire maternal mortality in the hospital during the period surveyed, it is obvious that this obstetric complication is worthy of thoughtful attention. An analysis of the series also reveals *interesting changes in obstetric practice during the years of the study, and a notable improvement in both maternal and fetal mortality as certain principles and procedures were put into effect.*

The cause of placenta previa is obscure, and in most respects this series throws no light upon it. In one regard, however, the figures are suggestive. In the obstetric admissions for the period surveyed, the proportion of multiparous to primiparous women was 1.7:1, whereas in the placenta previa cases it was 3.4:1. Some authorities have recently pointed out that parity does not predispose to placenta previa, but these proportions would seem to suggest that high parity may be of some etiologic significance. Frequency of gestation, furthermore, may play some part in the production of placenta previa, as may the occurrence of placenta previa in previous pregnancies. Seventy-one of the 202 multiparas in this series, 35.1 per cent, had had four or

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more pregnancies in rapid succession, and 9 had had placenta previa in previous pregnancies. One patient had had 3 placenta previas in four years.

No racial difference was noted in the incidence of placenta previa. One hundred five of the 260 patients were white and 155 colored, which is approximately the proportion one would expect in view of the disparity between white and negro obstetric admissions.

ROUTINE OF MANAGEMENT

The key to the successful management of placenta previa, all authorities agree, lies in the employment of a routine which is practical at all times and which is applicable to any emergency. Since such a routine has been put into effect on the obstetric services of Charity Hospital for all cases of vaginal bleeding late in pregnancy, the maternal mortality from placenta previa in that institution has decreased some 36 per cent. This improvement, which has been chiefly noted in the last two years, is to be compared with the decrease in the mortality from placenta previa in the United States over the same period, which, according to the Children's Bureau, has been only 5 per cent.

The routine employed includes prenatal instruction of the patient; prompt hospitalization at the first sign of bleeding; establishment of the diagnosis by vaginal examination under strict aseptic precautions, after all preparations have been made for immediate delivery; preparation for blood transfusion and its employment as indicated; and termination of the pregnancy by an appropriate method as soon as the diagnosis has been confirmed.

Prenatal Instruction.—When the patient informs the physician that she has experienced genital bleeding, the first requisite in the proper management of placenta previa has been accomplished. Patients of the type with whom we deal in Charity Hospital, however, are very likely to ignore slight bleeding, and to pay no attention to the amount of blood lost, unless they have been specifically instructed on these points. Such carelessness is particularly typical of negro women in any condition in which pain is not a prominent symptom. The proper instruction of our patients is, therefore, an important part of our management of placenta previa. We tell them plainly that any genital bleeding is potentially very serious, even though it is a mere spotting, and insist that it be reported immediately. Tragic experiences have convinced us, like other obstetricians, that the risks inherent in the initial bleeding, however slight it may be, are grave enough to warrant a presumptive diagnosis of placenta previa, which immediate steps should be taken to establish or confirm.

Hospitalization.—Placenta previa is an obstetric complication for which home management is not safe. Because serious hemorrhage may recur at any time, and because even a careful vaginal examination may produce furious bleeding, it is essential that the facilities, equipment, and personnel of a hospital should be at one's immediate command. We therefore make no examinations in the home, and refer all our patients to the hospital as soon as any bleeding occurs. We also advise patients who live out of the city to make the trip to the hospital. Many individuals in this series were safely transported for distances of 50 or 100 miles by train or automobile, and serious bleeding did not occur in a single case in which the condition had been suspected by the local physician and no examination or manipulation had been attempted in the home.

The trouble and expense of hospitalization are warranted by the serious possibilities inherent in vaginal bleeding late in pregnancy. Some 70 per cent of all the patients referred to Charity Hospital for hemorrhage after the sixth month in the period covered by this study were found to have placenta previa or the equally serious complication of abruptio placentae.

Diagnosis.—In our experience, 50 per cent of all cases of painless genital bleeding in the last trimester of pregnancy prove to be due to placenta previa. In this series the initial hemorrhage occurred prior to the twenty-eighth week of gestation

in 7 cases, 2.6 per cent; between the twenty-eighth and thirty-seventh weeks in 81 cases, 31.1 per cent; and after the thirty-seventh week in 172 cases, 66.3 per cent. In most instances the bleeding was painless, but in 44 cases, 16.8 per cent, it was associated with the onset of labor, or occurred after labor had begun, and in a few other instances it was possible to trace it to trauma following intercourse or douching, or to some accidental fall or injury.

The actual diagnosis of placenta previa can be made only when the spongy, cushiony mass of the low-lying placenta is palpated on digital examination. Yet in spite of the importance of immediate diagnosis and the fact that the cause of the bleeding can be definitely established only by vaginal examination, we do not undertake such an examination until the following preparations have been made:

1. Donors are available for transfusion and remain available until we ourselves dismiss them.
2. Every provision is made for the control of bleeding and for the immediate termination of pregnancy by the vaginal or abdominal route as indicated.
3. The patient is surgically prepared and every provision is made for the accomplishment of a gentle vaginal examination under a strictly aseptic technique.

Only vaginal examination, in our opinion, supplies adequate information in this condition. If digital examination is not conclusive and placental tissue cannot be palpated, it is our practice to insert a bivalve speculum to aid in the differential diagnosis of other causes of painless bleeding, such as erosions, varicosities, polyps, and malignancy. We have found rectal examination of little value, and several cases in this series, in which profuse hemorrhage occurred after it had been done, show that it causes even more trauma than vaginal examination. Also we never use enemas. The roentgenologic diagnosis of placenta previa by means of sodium iodide or air introduced into the bladder has not furnished conclusive evidence in our hands, and we are unwilling to rely upon it for accurate information. We consider amniography dangerous and never employ it.

Complete placenta previa, in which the entire os of the cervix is covered by the placenta, was present in 96 of our 260 cases, 37 per cent. Partial placenta previa, in which the placenta covers only a portion of the os, was present in 86 cases, 33 per cent. In practice, we state the exact portion of the os covered by the placenta in terms of 25, 50, and 75 per cent. Marginal placenta previa, in which the placenta borders on or touches the cervical os, was present in 78 cases, 30 per cent. In this study low implantation, in which the placenta is attached to the lower uterine segment but the edge is above the internal os, has been classified with marginal implantation. It is the least severe type, and is frequently overlooked if the bleeding is slight or if labor progresses rapidly.

TRANSFUSION

It is our practice to procure donors as soon as the patient enters the hospital and before internal examination or any other procedure is attempted, and to keep them available until it is quite certain that their services will not be immediately required. If there has been a serious loss of blood, a transfusion is given before diagnostic or therapeutic measures are instituted. If the blood loss has not been great, the sterile vaginal examination is proceeded with and transfusion is done if hemorrhage ensues or as the need becomes evident during treatment. In most instances the measure is deferred until after delivery, when it is now our practice to employ it routinely. The patient may require one transfusion or several, depending upon the estimate of the amount of blood lost. In the average case we usually give 650 c.c. of blood.

A study of the Charity Hospital figures furnishes conclusive proof of the value of transfusion in placenta previa. Only 34 per cent of the 260 patients who com-

prise the series were transfused. On the other hand, 88 per cent of the patients with placenta previa seen during the last two years were transfused, as was every patient seen during the last year, and the notable improvement in mortality closely parallels the increasing use of blood. In many of these cases, in our opinion, puerperal infection was prevented by the early correction of anemia.

The administration of blood is the only method of permanently correcting blood loss, but if blood should not be immediately available, the depleted body fluids may be temporarily restored by the use of glucose solution (500 c.c. in 10 per cent concentration) or acacia solution (500 c.c. in 6 per cent concentration) introduced by vein, or by the introduction of 1,000 c.c. of Ringer's solution by hypodermoclysis. The parenteral administration of fluids usually improves the clinical picture, but such patients should always be carefully observed until blood is available, for a false sense of security may be created and shock may occur several hours after the good effects have worn off.

METHODS OF DELIVERY

There is no expectant treatment of placenta previa. As soon as the diagnosis is confirmed by vaginal examination, the appropriate method for terminating pregnancy should be instituted, without regard for the viability of the child. As a matter of fact, the fetal prognosis is not improved by a waiting policy, and the maternal prognosis is made very much worse. Nine of the 20 maternal deaths in this series occurred in patients who had been bleeding for more than 5 days, and in no instance was a live child secured.

We endeavor to individualize our patients, and have no set plan for accomplishing delivery in these cases. Certain general principles, however, determine our course. The selection of the method of intervention is dependent upon such considerations as the type of placenta previa, the condition and parity of the patient, the stage of pregnancy, and the status of the fetus. The experience and ability of the obstetrician, and the facilities and amount and kind of equipment available, unfortunately cannot always be ignored. If by ill chance the patient is not in a hospital and cannot be admitted to one, we believe that major obstetric procedures should never be attempted.

Whatever form of therapy is adopted is directed toward: (1) the control of hemorrhage; (2) the replacement of blood loss; (3) the selection of the most rapid method, compatible with safety, of terminating the pregnancy; (4) avoidance of trauma; and (5) prevention of infection.

DELIVERY FROM BELOW

One hundred and sixty-two patients, 62.3 per cent, were delivered by the vaginal route, with a maternal mortality of 11.1 per cent and a gross fetal mortality of 45.7 per cent. The following methods were employed:

Rupture of the membranes in 80 cases (60 marginal, 20 partial) with a maternal mortality of 5 per cent and a fetal mortality of 27.5 per cent.

Willett's method of scalp traction in 6 cases (4 partial, 2 marginal) with 0 maternal mortality and a fetal mortality of 16.6 per cent.

Breech traction in 5 cases (3 partial, 2 marginal), with 0 maternal mortality and a fetal mortality of 20 per cent.

Metreurysis in 40 cases (11 complete, 19 partial, 2 marginal) with a maternal mortality of 12 per cent and a fetal mortality of 62.5 per cent.

Braxton Hicks' version in 21 cases (8 complete, 10 partial, 3 marginal) with a maternal mortality of 24 per cent and a fetal mortality of 80.9 per cent.

Vaginal tamponade in 10 cases (4 complete, 5 partial, 1 marginal) with a maternal mortality of 40 per cent and a fetal mortality of 80 per cent.

Even a casual survey of these figures makes it clear that the first three methods are far safer for both mother and child than the last three. On the other hand, although rupture of the membranes, Willett's scalp traction, and breech traction are simple and safe methods in themselves, part of their apparent good results in this series must be attributed to the fact that they were used in the management of the

simpler cases of placenta previa. There is no doubt, however, that metreurysis, Braxton Hicks' version, and vaginal tamponade are actually or potentially dangerous, and it is not surprising to find in the later years of this study that many cases in which they would once have been employed were managed by cesarean section.

Rupture of the membranes is a simple and effective method in the less serious cases of incomplete placenta previa, though in our opinion it is rarely suitable for the management of the complete type. It is also the first step in any mode of intervention which aims at delivery through natural channels. The release of the amniotic fluid permits the presenting part to descend into the pelvis, and bleeding is thus controlled by a sort of natural tamponade. We have found that the degree of compression can be materially increased by the application of a tight abdominal binder. If the patient is not having pains, we endeavor to precipitate labor by the administration of pituitary extract (1 minim doses at twenty-minute intervals).

Willett's method of scalp traction was devised for cases in which the child is dead or nonviable, but we have used it several times recently on living children, with excellent results. If bleeding continues after rupture of the membranes, in primary breech presentations, a foot may be brought down and slight traction exerted to compress the placenta by the buttocks against the uterine wall.

Braxton Hicks' version, which should not be confused with the simple and safe method of breech traction just described, is still useful in emergencies, when the child is dead or previable, or when other methods for the control of hemorrhage cannot be employed. It is, however, a difficult and dangerous maneuver, and we do not recommend it. A vaginal pack is not an effective method for the control of hemorrhage, and its introduction, like the introduction of a bag into the uterus, predisposes to infection. If metreurysis should be employed, we prefer intraovular insertion of the bag, because it permits its close application against the placenta, and we always use the largest size (11 cm.), so that the cervix will be sufficiently dilated after the bag has been extruded to permit immediate delivery of the child, by forceps or by version and slow extraction if spontaneous delivery does not seem imminent. We also prefer manual traction to traction by weights, because unregulated force is likely to result in tears of the friable tissues of the lower uterine segment.

MANAGEMENT OF THE THIRD STAGE OF LABOR

Active treatment was required after delivery in 44, 27 per cent, of the 162 patients in this series who were delivered by the vaginal route. Four required more than one procedure to control the hemorrhage. Manual removal of the placenta was done in 12 cases, repair of lacerations in 17, and packing of the uterus in 19.

These figures are significant, for it is often not realized that complications of the third stage of labor and of the post-partum period may contribute materially to the mortality of placenta previa. Hemorrhage may follow the birth of the baby or the expulsion of the placenta, but may not occur until several hours or even several days after delivery. It may originate from the placental site or from lacerations of the birth canal. It is not always possible to prevent post-partal hemorrhage in placenta previa, but if the possibility is realized and the bleeding recognized as soon as it occurs, and managed properly, it is rarely of serious consequence.

DELIVERY BY ABDOMINAL SECTION

The data from Charity Hospital are in accord with reports in the literature as to the increasing use and real value of cesarean section in the management of placenta previa. It was used in 27 per cent of the cases in the first five years of this survey, and in 45 per cent in the second five years. During the second period 91 per cent of all cases of complete placenta previa were managed by the abdominal route, against 55 per cent in the first period. The relative mortalities of 5.1 per cent for the last five years and 11.3 per cent for the first period testify to the wisdom of the increasing use of this method.

The figures from Charity Hospital also illustrate the increasing use of laparotrachelotomy. This operation was used in only 31 per cent of the cases of placenta previa managed by abdominal section prior to 1934, but in 52 per cent of the cases

seen since then, and in the last year, it was used routinely in deliveries by the abdominal route. Laparotrachelotomy has several distinct advantages over the classical type. It furnishes rapid, direct access to the field of bleeding. It is associated with less risk than the classical section in potentially infected cases. There is less likelihood of rupture of the uterus in subsequent pregnancies, because the scar is in the noncontractile portion. Our experience has shown that post-partal hemorrhage is not likely to occur after cesarean section if a tight gauze pack is inserted into the uterus through the uterine incision and kept in place for eight hours.

In patients who are obviously infected from unsterile examination or improper maneuvers, the Porro operation has a distinct field of usefulness. It was employed in 9 patients in this series, in 3 of whom the presence of fibroids furnished an additional indication for hysterectomy.

MATERNAL AND FETAL MORTALITY

The mortality reported for placenta previa varies according to circumstances. In the practice of an experienced obstetrician it is likely to be low among patients whose pregnancies he has supervised throughout, and it is usually low in well-organized maternity clinics in which prenatal care is adequate. Neglected patients supply the major portion of both fetal and maternal mortality. In this connection, it is significant that at Charity Hospital the maternal mortality for the whole series of 260 cases was 7.6 per cent, but that, when the figure was broken down, the white mortality was found to be 5.7 per cent and the negro 9 per cent.

The condition of the patient is an extremely important factor in the mortality. In 3 of the fatal cases in this series, the patients were admitted in shock. One other patient was moribund on admission, and one was gravely ill with pneumonia, which had been present for two weeks. It is significant that the 3 patients admitted in shock, as well as the patient admitted moribund, had been examined at home, with no preparations to control the furious hemorrhage which resulted in each case. In 5 of the fatal cases the condition of the patients was fair on admission, and in 10 it was good, which introduces the immediate implication that the management of these cases, and not the placenta previa per se, was responsible for the fatal outcome.

The causes of death in the Charity Hospital series agree with those listed in practically every report in the literature. Nine patients died from hemorrhage, 6 from rupture of the lower uterine segment, 4 from infection, and 1 from pneumonia. Some of these deaths were clearly due to the traumatic manipulations used to control hemorrhage, which resulted in rupture of the uterus or the introduction of infection. It is significant, for instance, that of the 5 deaths following Braxton Hicks' version, 3 were due to rupture of the uterus and 2 to hemorrhage, and that in some of these cases immediate extraction had been attempted after the version, without regard to the degree of dilatation.

Another consideration in the maternal mortality in this series from Charity Hospital also deserves emphasis. The general maternal mortality in the 260 cases was 20, 7.6 per cent. But the rate in delivery from below was 11.1 per cent, more than five times higher than the rate in delivery by cesarean section, 2.0 per cent. Only 2 patients died after cesarean section, both from puerperal infection, one after high and one after low section. In the 73 cases of complete placenta previa terminated by section there was one death, 1.3 per cent, against 8 deaths, 35 per cent, in the 23 cases handled from below. These disproportions are all the more significant when it is recalled that the most serious cases were handled by cesarean section. On the other hand, these favorable figures should not lead to the use of abdominal section in all cases of placenta previa. The proper selection of cases will give better results than the routine and indiscriminate use of this method.

The gross fetal mortality was 32.3 per cent and the corrected fetal mortality 13.8 per cent. In many instances the babies were dead when the mothers were admitted, or were previable, and much of the fetal mortality was therefore unpreventable. A further correction might well be made for the large number of premature and immature infants who were delivered alive but did not survive.

Both the total (32.3 per cent) and the corrected (13.8 per cent) fetal mortality were less in the complete type of placenta previa (29.1 per cent, 10.4 per cent) than in the partial variety (38.3 per cent, 17.4 per cent). This disparity is explained by the fact that most cases of complete placenta previa were managed by cesarean section, in which the child's chances of life are enhanced.

At Charity Hospital the fetal mortality was 5.1 per cent in the cases managed by cesarean section, against 19.2 per cent, almost four times as much, in the patients delivered by the vaginal route. It is only fair to add, however, that in some of these cases the status of the fetus on admission seems to have been the factor in deciding upon vaginal rather than abdominal delivery.

SUMMARY AND CONCLUSIONS

1. A series of 260 consecutive cases of placenta previa is reported from Charity Hospital of Louisiana at New Orleans for the 10-year period ending Jan. 1, 1939. The maternal mortality was 7.6 per cent, the gross fetal mortality 32.3 per cent, and the corrected fetal mortality 13.8 per cent.

2. A definite routine is outlined for the management of bleeding in the last trimester of pregnancy, including: immediate hospitalization for diagnosis and treatment at the time of the first hemorrhage; confirmation of the diagnosis by vaginal examination under strict aseptic precautions, after every provision has been made for the control of hemorrhage and for any type of delivery; the immediate termination of gestation when the diagnosis of placenta previa has been established; preparation for transfusion before any vaginal examination or manipulation is attempted.

3. It is emphasized that no patient is likely to die from the first hemorrhage or from the delay necessary for the preparations outlined if internal examination or manipulation has not been attempted.

4. It is also emphasized that blood losses should be corrected by transfusion in every case of placenta previa, and that donors should be kept available until there is no longer any possible need for their services.

5. Rupture of the membranes, control of hemorrhage by Willett's scalp traction or by breech traction, metreurysis, Braxton Hicks' version, and vaginal tamponade were used in the 162 cases in this series in which delivery from below was employed. The last three methods, which give results far inferior to the first three, and which are potentially dangerous, are no longer very generally employed. There was noted an increasing tendency to employ cesarean section, particularly the low operation, in most cases of complete and many cases of partial placenta previa. It offers the best prognosis for the child, and in competent hands and properly selected cases is quite safe for the mother.

6. Deaths in placenta previa are chiefly due to hemorrhage, sepsis, and rupture of the lower uterine segment. These causes are largely preventable, and such deaths continue to occur, chiefly because patients delay seeking medical consultation and because many physicians are not fully aware of the potential seriousness of all hemorrhage in the third trimester of pregnancy and are unprepared to handle this complication.

PLACENTA CIRCUMVALLATA

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ALTHOUGH during the past sixty years much investigation has been done in the study of placental pathology, many questions are still unanswered and much information is yet to be obtained before this transient, intermediary organ between mother and fetus, is clearly understood. The recent study of Streeter of the developing monkey ovum, offers a very valuable approach to the solution of many of these problems.

There are, however, many lesions of the placenta which may be clarified with the information available today. It is our desire to call attention to one particular variety of placental abnormality, viz., placenta circumvallata, and to attempt to elucidate some of the widespread confusion regarding its clinical significance.

We have as a basis for our exposition a study of the clinical histories and pathologic examinations of 150 cases of definite placenta circumvallata, observed in 20,720 deliveries. Only single pregnancies have been considered. All cases of marginal infarction, placenta marginata, and other forms simulating the gross appearance of placenta circumvallata have been carefully excluded.

In 1934, Hobbs and Rollins, noting the frequent association of this condition with certain clinical phenomena, reported their study of the first 79 cases of this present series.

Placenta circumvallata may be defined as an abnormal development of the placenta, characterized by a restricted growth of the chorionic plate, with oblique growth of its marginal villi into the surrounding decidua vera to form an extrachorial margin of placental tissue around part or all of its circumference. The membranes which insert into the edge of the plate become reduplicated and form a fold lying on the plate and constitute a wall of varying thickness around it.

If the fold is not present, the condition is commonly spoken of in the German literature as placenta marginata. The term placenta circumvallata is reserved for the type with the fold of membranes and is considered as only a further development of the secondary changes incident to the limit of growth of the chorionic plate.

The number of terms used in the literature to designate this condition is altogether too numerous and most confusing. Williams pointed out the need for simplification of the terminology. Some of the most common terms found in the literature will be mentioned so that there will be a clear understanding of the nomenclature.

In the American literature the term placenta circumvallata is most widely used. DeLee uses the term "neppiformis" synonymously with circumvallata. Goodall

uses placenta circumvallata in the usual sense and has added the term circumcrescent to designate the type without the fold of membranes which corresponds to the marginata of the German literature.

The most frequently used designations in the German literature, which is by far the largest on the subject, are placenta marginata and placenta circumvallata as given in the definition above. Robert Meyer, who has studied some 300 specimens, suggested using the term placenta extrachorialis. This term, although quite descriptive, has not been widely accepted. The French use the terms marginé, Brodé and collarette.

This confusion of names and their application is reflected in the wide discrepancy of the incidence of the abnormality, as reported by various authors. Williams found it occurring in 1 to 2 per cent of his cases, von Herff 7.6 per cent, Bertkau 14 per cent, and Del Vivo 21.3 per cent. We have found the incidence of placenta circumvallata to be 0.8 per cent in single pregnancies.

The theories of etiology and the method of formation of this anomaly have been described in detail by Williams and generally accepted.

A thorough understanding of the developmental anatomy is indispensable for the intelligent discussion of the clinical significance of this abnormality. To emphasize the importance of this aspect we will quote two leading authorities.

Williams, who studied some 30 cases of term and near term specimens, states, ". . . upon going over the clinical histories of patients presenting the abnormality, my impression is that it is practically without clinical significance." On the other hand Seitz in Stoeckel's Lehrbuch der Geburtshilfe for 1935, states, "Placenta marginata (German terminology for circumvallata) has certainly a definite clinical significance. One has ground to state that in pregnancy protracted bleeding and many abortions have their cause in this irregularity of the placenta. Also difficulty is more often encountered in the third period when complicated by placenta marginata." Hinselman, Sarway and Bumm, and other leading German authorities are of the same opinion, while in this country, Williams' opinion has been generally accepted and recorded in our leading textbooks and references. DeLee and Goodall have stated that this condition may cause clinical complications without giving any factual data. We have been unable to find a report of a clinical study of this abnormality.

It is very important to obtain accurate information concerning this abnormality. Is it an etiologic factor in abortion? Does it cause last trimester bleeding which might be confused with the bleeding from placenta previa? Is it responsible for some fetal deaths? Does it cause difficulty in separation of the placenta? Is it dangerous to the mother? How shall such cases be managed?

In this study of 150 cases, we believe that we have a large enough series to give some accurate information. Several factors must be considered in determining the outcome in cases of placenta circumvallata: (1) The period of pregnancy when the chorionic plate becomes restricted; (2) the degree of restriction; (3) the percentage of circumferential restriction; (4) the functional reserve of the placenta at the time this condition occurs; (5) subsequent reduction of the placental function by infarction, etc.; (6) the ability of the trophoblast

to create new placental spaces; and, (7) the irritability of the uterus. The outcome is dependent on the time, degree, and multiplicity of these factors.

In considering the clinical aspects of this anomaly, naturally one's attention is directed to: First, the effect on the fetus, and second, the effect on the mother.

To those who are familiar with the development of placenta circumvallata, it is obvious that the fetus may be affected in the following ways: First, restriction of the growth of the plate and the inability of the villi to create new placental spaces sufficient to meet all the increasing demands of the fetus, may lead to death. This placental deficiency may be augmented by placental infarction. If the fetus perishes early, abortion will occur. Later in pregnancy the placental reserve may be used up and the fetus may die just before term. Under ideal conditions the placental reserve may be sufficient to carry the fetus to term. This not infrequently happens and accounts for the report of Williams where only term or near term placentas were examined.

If one has examined the extrachorial margin of a circumvallate placenta, it will be recalled that the fetal surface is bounded not by the strong chorionic plate, but by the delicate decidua and overlying membranes. Motion of the uterus when this area is under tension in an attempt to keep pace with the expanding placental site may easily cause a rupture through the decidua into the intervillous spaces and thereby produce bleeding which may be concealed if the uterine cavity is obliterated or it may be revealed by dissecting the membranes from the decidua vera. Fortunately the blood pressure in the intervillous spaces is very low so that the bleeding is rarely, if ever, alarming. From this disturbance of the pregnancy, premature labor is often induced. If the child has reached the viable period, it is frequently born alive, provided there has been adequate placental function until this accidental hemorrhage initiated labor. Abortion, death of the fetus and premature labor are complications that may occur in cases of placenta circumvallata.

The usual effects on the mother are as follows: (1) Hemorrhage from incomplete abortion, although these abortions are usually complete, because they occur after the placenta has developed. (2) Blood loss from rupture of the marginal intervillous spaces as described above. It causes irregular, painless bleeding simulating placenta previa, especially if it occurs during the last trimester of pregnancy. (3) Occasional difficulty in the separation of the placenta because of the abnormal growth of the villi deeper into the decidua and occasionally into the uterine muscle.

SUMMARY

Table I is a composite picture of the 150 cases studied.

1. The duration of pregnancy is classified according to the number of weeks when known, as follows: under 27 weeks are abortions; 27

TABLE I.* A COMPOSITE PICTURE OF A CLINICAL AND PATHOLOGIC STUDY OF 150 CASES OF PLACENTA CIRCUMVALLATA OCCURRING IN 20,720 CONSECUTIVE DELIVERIES, AN INCIDENCE OF 1 TO 138 OR 0.8 PER CENT

CLINICAL CLASSIFICATION	FETAL MORTALITY			TYPE OF CIRCUMVALLATION		AVERAGE DURATION OF PREGNANCY WEEKS	PARITY		PRE-LABOR BLEEDING CASES	RETAINED PLACENTA		WASSERMANN	
	STILLBORN OR DIED IMMEDIATELY	SIZE FOR VIABILITY (117 CASES)	TOTAL	COMPLETE PER CENT	PARTIAL PER CENT		PRIMIPARAS	MULTIPARAS		PERIODS OF GESTATION	TOTAL	PERIODS OF GESTATION	TOTAL
Abortions 33 cases 22%	33 cases 100%	16 deaths, 14%	49 babies, 33%	51	49	24	10 cases 33%	23 cases 67%	18	6 cases 18%	12 cases 8%	Negative, 19 cases Positive, 4 cases Unknown, 10 cases 17% of known have positive serology	107 known cases 25% positive serology
Prematures 23 cases 16%	9 cases 39%			38	62	31	7 cases 33%	16 cases 67%	6	1 case 4%		Negative, 17 cases Positive, 3 cases Unknown, 3 cases 15% of known have positive serology	
Term 94 cases 62%	7 cases 7%			41	59	39	28 cases 30%	66 cases 70%	9	5 cases 5%		Negative, 44 cases Positive, 20 cases Unknown, 30 cases 31% of known have positive serology	

*Abortion, fetus weighing under 1500 gm. and less than 25 cm. in length.
Prematures, fetus weighing between 1500 and 2500 gm., and between 25 and 45 cm. in length.
Term, fetus weighing over 2500 gm., and over 45 cm. in length.

to 38 weeks are premature; and, 38 to 42 weeks are term deliveries. This method is obviously quite inaccurate so the weight-length measurements were also used as defined beneath the table.

2. The incidence of abortion and premature labor is very high as compared to the average group of pregnant women. It must be kept in mind that this group of 150 women, other than the abnormality of the placenta, represents a typical sample of clinic and private practice.

3. A fetal mortality of 14 per cent in babies born after the twenty-seventh week emphasizes the seriousness of placenta circumvallata. A total mortality of 33 per cent places this abnormality as one of the outstanding feticides.

4. We have classified all of the specimens either as complete or partial circumvallata. On first consideration one would think that the complete type would be much more effective in producing complications during pregnancy. However, when one considers that the majority of the partial variety included 50 per cent or more of the circumference and many were almost complete, it can be understood why they are as effective as the complete variety in causing complications.

5. The average duration of pregnancy for the series is 32.5 weeks. Some German authors claim that postmaturity is frequently associated with this condition. We cannot substantiate this observation. Most labors occurred around the twentieth week.

6. For some unknown reason parity plays a role in the occurrence of placenta circumvallata. Multiparas outnumbered primiparas about two to one in each classification. A count of primaparas and multiparas in successive deliveries in the St. Louis Maternity Hospital for a year showed approximately equal numbers. The youngest patient in this series was 18 years old and the oldest was 42.

7. We wish to call attention especially to the uterine bleeding produced by this condition. Thirty-three cases showed prelabor bleeding. It was painless, intermittent in character; although it lasted several weeks at a time, it was usually mild. It occurred at any time during pregnancy and was not always followed by the onset of labor. Many patients bled intermittently for many weeks and delivered a live infant at term. In none of the patients was the bleeding serious, and with bed rest and sedation there was a tendency for cessation of bleeding. If the fetus perished, labor usually soon followed.

The most important clinical aspect of this condition is the awareness that painless bleeding during the last trimester is not always pathognomic of placenta previa. A few of these cases were brought into the hospital with that tentative diagnosis. Vaginal examination failed to confirm the diagnosis of placenta previa, and with bed rest the bleeding usually ceased. Unlike placenta previa, bleeding from a circumvallate placenta does not tend to be more severe with each recurrence. It is extremely important to be aware of this condition, for although there is little to be done for these patients, it is a serious mistake to treat them actively for the mistaken diagnosis of placenta previa.

8. Twelve patients had retained placentas. These cases were handled in the usual conservative manner. After a reasonable period of time, manual removal was necessary.

9. The incidence of syphilis (25 per cent of 107 known cases) was about twice the average in the clinic population. Many of these cases were under antisyphilitic treatment before the onset of pregnancy, and all syphilitic patients received treatment as soon as diagnosed, no matter what the stage of pregnancy. The etiologic relationship, if any, of syphilis to the formation of placenta circumvallata is not clear.

10. Hunt reported two cases of hydrorrhea gravidarum associated with placenta circumvallata. In our series four definite cases were noted. In a previous article by one of us, a picture of the placenta of such a case was recorded. We have a placenta, which is not included in this series, since it was delivered after the compilation of these statistics, from a woman who had an intermittent discharge of large amounts of fluid from the sixth month until term. It appears that hydrorrhea gravidarum is frequently associated with this condition.

CONCLUSIONS

From a study of this series of 150 cases of placenta circumvallata, we feel justified in making the following conclusions:

1. The occurrence of this abnormality is much less frequent than most writers have stated. As a result of confusion in terminology and lack of definite criteria for identification, many cases of marginal infarction, etc., have been reported as cases of circumvallation. The incidence of the anomaly in our series is 0.8 per cent.

2. It is of considerable clinical significance. It frequently terminates in an abortion (22 per cent). It often causes premature labor (16 per cent). The mortality is high (33 per cent). Painless bleeding, which occurred before the onset of labor, happened in 22 per cent of the cases. When the bleeding appeared during the last trimester of pregnancy it was mistaken for placenta previa in some instances.

3. In cases of hydrorrhea gravidarum this abnormality should be suspected.

REFERENCES

(1) *Adair and Thelander:* Am. J. Obst. & Gynec. **10:** 172, 1925. (2) *Bayer:* Beitr. z. Geburtsh. u. Gynäk. **16:** 1, 1911. (3) *Bumm:* Grundriss zum Studium der Geburtshilfe, ed 15, p. 412, 1922. (4) *Burkan:* Charité-Ann. **36:** 440, 1912. (5) *Dees-Mattingly:* Am. J. Anat. **59:** 485, 1936. (6) *Del Vivo and Corinaldes:* Ref. Ber. ü. d. ges. Gynäk. u. Geburtsh. **8:** 755, 1926. (7) *DeLee:* Principles and Practice of Obstetrics, ed. 6, Philadelphia, 1934, W. B. Saunders, p. 603. (8) *Dippel:* Bull. Johns Hopkins Hosp. **54:** 24, 1934. (9) *Goodall:* Am. J. Obst. & Gynec. **28:** 707, 1934. (10) *Hinselman:* Halban-Seitz, Biol. u. Path. der Weibes **5:** 364, 1926. (11) *Hobbs and Rollins:* Am. J. Obst. & Gynec. **28:** 78, 1934. (12) *Hunt:* Proc. Staff Meeting Mayo Clin **28:** 78, 1935. (13) *Lahm:* Arch. f. Gynäk. **121:** 306, 1924. (14) *Liepmann:* Ibid. **80:** 306, 1906. (15) *Meyer:* Ibid. **84:** 542, 1909. (16) *Meyer:* Ibid. **98:** 493, 1912. (17) *Sarway, O.:* Handbuch der Geburtshilfe, ed. 3, **1:** p. 159. (18) *Schortz:* Arch. f. Gynäk. **27:** 15, 1886. (19) *Seitz:* Stoeckel Lehrbuch d. Geburtshilfe, p. 581, 1935. (20) *Strassmann:* Arch. f. Gynäk. **67:** 112, 1902. (21) *Streeter:* Am. J. Obst. & Gynec. **36:** 747, 1938. (22) *Thoms:* Ibid. **17:** 176, 1929. (23) *Veit:* Volkman's Sammlung Klin. Vort. **13:** 254, 1885. (24) *von Herff:* Ztschr. f. Geburtsh. u. Gynäk. **15:** 268, 1896. (25) *Vorpin:* Am. J. Obst. & Gynec. **23:** 551, 1932. (26) *Williams:* Ibid. **13:** 1, 1927.

A STUDY OF CERVICAL POLYPS

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THE universal proof that hyperplasia of the endometrium is of estrogenic origin served to intensify interest in the possible existence of an etiologic relationship between other pathologic conditions of the uterus and abnormal hormonal states.[1] To maintain, however, that the coexistence of either benign or malignant tumors of the uterus and endocrine disorders is more than mere coincidence, implies a greater certainty than the facts yet warrant. Clarification of this important problem may be attained, as indicated in several recent studies on myoma[2] and carcinoma[3] of the uterine body, through detailed analysis of all factors related to uterine tumors. In pursuance of this thought, the various clinical and pathologic aspects of cervical polyps are herein considered.

The present report comprises a group of 117 consecutive patients with cervical polyp observed at the Mount Sinai Hospital during the period between Jan. 1, 1933 and Dec. 31, 1937. Of the 117 patients, 21 were treated in the outpatient department and 96 were hospitalized.

FREQUENCY

Reports on the incidence of cervical polyps as a gynecologic entity vary according to the source of the data. For instance, in an analysis of tissues removed during 1,000 consecutive gynecologic operations, Fetterman[4] found a 10 per cent incidence of cervical polyps. A study by Geiger,[5] on the other hand, of 2,048 gynecologic patients admitted to a tumor clinic revealed only 1.5 per cent of cervical polyps. Ninety-six of the 117 instances of cervical polyps herein reported were encountered in 3,900 hospitalized patients who underwent gynecologic operations, an incidence of 2.4 per cent.

The usually benign character of a cervical polyp, its ease of removal, and the permanence of such treatment make it a minor gynecologic lesion and relegate it to the limbo of "office gynecology." For this reason, its actual frequency cannot be ascertained from statistics based entirely on hospital experience. Elsewhere[6] it was noted that 23 women with cervical polyps were found among 163 patients with irregular uterine bleeding examined in office practice—an incidence of 14.1 per cent. This higher frequency of cervical polyps, when viewed from the standpoint of the leading symptom, augments their clinical importance.

AGE INCIDENCE

While the occurrence of a cervical polyp is not limited to any age period, 41 per cent in the present series were found during the fifth decade (Fig. 1). This is in accord with the earlier reports of Schroeder,[7] Fluhmann,[8] and Geiger.[5] The climacteric, denoting the natural decline of ovarian function, does not protect the woman from the cervical polyp. Forty-five of these 117 women (39.3 per cent) came under observation after the menopause.

Childbearing has an apparent influence on the incidence of cervical polyps, inasmuch as 99 of the 117 patients (84.6 per cent) had borne one or more children (Table I).

TABLE I. INFLUENCE OF PARITY ON THE INCIDENCE OF CERVICAL POLYPS IN 117 PATIENTS

PARITY	NUMBER OF PATIENTS	PERCENTAGE
Multiparous	90	77.0
Primiparous	9	7.6
Nulliparous	18	15.4

SYMPTOMS

In the present series of 117 patients with cervical polyps, 60 (51.3 per cent) had abnormal uterine bleeding, 14 (12 per cent) complained of leucorrhea, and 43 (36.7 per cent) were free from symptoms attributable to polyps. In the latter group, the polyps were discovered during routine examination. This fact coupled with the frequency with which polyps complicate other gynecologic lesions makes it difficult to determine the precise significance of the cardinal symptoms of cervical polyps, namely, abnormal uterine bleeding and leucorrhea.

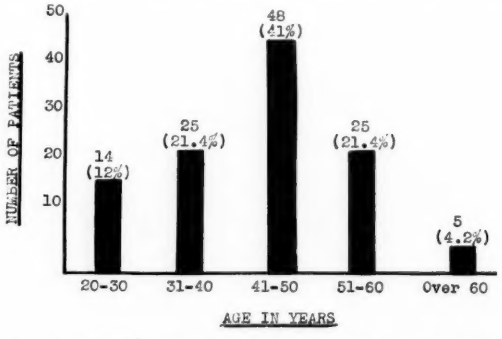

Fig. 1.—Age incidence of cervical polyps in 117 patients.

The abnormal bleeding, often the portentous signal of genital carcinoma, lends clinical dignity to the cervical polyp. Except in instances of vaginal bleeding following coitus or douching (contact bleeding), of which there were only 10 in this series, the source of the bleeding is not always clear. This is especially true when an associated pathologic condition such as uterine myoma is present. It is, moreover, possible that bleeding, in some instances, may arise from a hyperplastic endometrium and not from the polyp. The two conditions may, according to Geist,[9] have a single endocrine etiology—a theory which still seems to have more of shadow than of substance.

Either menorrhagia or metrorrhagia may occur, but the latter is more likely to be caused by the polyp alone. Of the 60 patients with abnormal uterine bleeding in the present group, 40 had metrorrhagia, 13 menorrhagia, and 7 had both. It is noteworthy that 16 of the 40 patients with metrorrhagia were beyond the menopause.

The low incidence (12 per cent) of pronounced leucorrhea as a leading symptom seems unusual, especially in view of the frequent coexistence of cervical polyps and chronic cervicitis (Table II). It emphasizes, perhaps, the tendency of women to look lightly upon the presence of leucorrhea.

ASSOCIATED GYNECOLOGIC CONDITIONS AND ETIOLOGY

Cervical polyps are often dwarfed into insignificance by coexisting symptom-producing pelvic lesions (Table II).

Etiologically, the coexistence with cervical polyp of vaginal relaxation, uterine myoma, pregnancy, chronic pelvic inflammatory disease, and ovarian cystadenoma

TABLE II. INCIDENCE OF GYNECOLOGIC CONDITIONS ASSOCIATED WITH CERVICAL POLYPS IN 117 PATIENTS

ASSOCIATED GYNECOLOGIC CONDITION	*NUMBER OF PATIENTS	PERCENTAGE
None	34	29.0
Chronic cervicitis	73	62.4
Relaxation of vagina (cystocele, rectocele, and uterine descent)	20	17.0
Uterine myoma	10	8.5
Pregnancy	5	4.2
Chronic pelvic inflammation	4	3.4
Ovarian cystadenoma	1	0.8

*Two or more associated pelvic conditions were present in 30 patients (25.6 per cent), thereby accounting for a total number more than 117 in this table.

is of little importance because the respective incidence of these conditions in this group of 117 polyp-bearing patients is comparable to that found in any similar group of women. The absence, however, of an accompanying pelvic condition in 29 per cent of the patients is significant and bespeaks an independent origin of cervical polyp. Nor is the latter conception invalidated by the apparently overshadowing incidence (62.4 per cent) of chronic cervicitis as a coexisting lesion. This is supported by the fact that 99 of this series (84.6 per cent) were parous women, a group in whom the incidence of cervicitis is customarily high. Nevertheless, the higher incidence of both cervical infection and polyps in parous women suggests that the cervical trauma of childbirth may be the common etiologic denominator of both conditions.

The belief that a cervical polyp is a neoplasm, the growth of which is perhaps influenced by trauma sustained through childbearing, does not necessarily preclude the possibility of a causative endocrine factor. For that reason, an attempt was made to analyze the possible relationship of cervical polyp to endometrial hyperplasia, the one pelvic condition of proved estrogenic origin. Endometrial hyperplasia was present in only 11 of 40 women (27.5 per cent) who were curetted at the time of removal of the polyps. Nine of these 11 patients with coexisting endometrial hyperplasia were, moreover, in the fifth decade of life, when the incidence of endometrial hyperplasia, independent of other genital lesions, is ordinarily high.[10] The finding of an atrophic endometrium in 11 additional patients (27.5 per cent), all of post-menopausal age, emphasizes the widely diversified endometrial patterns found in association with cervical polyps and the nonendocrine etiology of the condition (Table III).

TABLE III. ENDOMETRIAL PATTERN IN 40 PATIENTS WITH CERVICAL POLYPS

ENDOMETRIUM	NUMBER OF PATIENTS	PERCENTAGE
Hyperplastic	11	27.5
Hypoplastic (atrophy)	11	27.5
Premenstrual (secretory)	10	25.0
Decidua	5	12.5
Proliferative (interval)	3	7.5

PATHOLOGY

The term cervical polyp includes all wholly or partially pedunculated tumors of the cervix, which often tend to project into the vagina on a long pedicle. Usually, they arise as mucous polyps from the endocervix near the internal os. A characteristic feature of the microscopic appearance of a cervical polyp is the fidelity with which the structure of the endocervix is reproduced. The histologic architecture of the cervical polyp is always more or less altered by the presence of certain secondary pathologic changes which, in the present group, included inflammation, cyst formation, epidermization, carcinoma, decidual reaction, edema, and excessive fibrous tissue (Table IV).

TABLE IV. INCIDENCE OF SECONDARY PATHOLOGIC ALTERATIONS IN THE CERVICAL POLYPS OF 117 PATIENTS

HISTOLOGIC PATHOLOGY OF POLYP	*NUMBER OF PATIENTS	PERCENTAGE
Inflammation	81	69.2
Cyst formation	14	11.9
Epidermization	10	8.5
Fibrous	9	7.6
Edema	4	3.4
Decidual reaction	3	2.5
Carcinoma	2	1.7

*The total number is more than 117 in this table because more than one of the histologic changes coexisted in several patients.

Chronic inflammation, recognized by diffuse or localized collections of lymphocytes and plasma cells, is unquestionably the most common histologic picture encountered in cervical polyps. It was present in 81 of the 117 specimens (69.2 per cent). The protrusion of the cervical polyp through the external os, interfering with its blood supply and exposing it to friction, predisposes it to ulceration and infection. The inflammatory reaction, always more acute at the tip of the polyp, usually includes polymorphonuclear leucocytes in areas where the surface epithelium had been lost.

The columnar epithelium covering the surfaces and lining the glands of a cervical polyp is susceptible, in common with the epithelial elements of the endocervix as a whole, to substitution by stratified squamous epithelium. This benign process, known as *epidermization,* is especially likely to occur in cervical polyps because of exposure, ulceration, and infection. The exact pathogenesis of epidermization in endocervical polyps is unknown. Clarification of the problem is hampered by our ignorance concerning many of the factors involved in the growth of cells. At least five theories have been formulated to account for the mechanism of epidermization, the simplest of which regards the process as the result of growth of basal cells from either adjacent squamous epithelium or subjacent squamous cell-rests.[11] It is probably, as Meyer[12] suggests, a reparative process. The conception that epidermization represents a true metaplasia, implying the actual conversion of mature columnar cells into squamous epithelium, is open to question.

While divergent views are held concerning the exact origin of epidermization in cervical polyps, unanimity of opinion exists regarding its ordinarily benign character.[12, 13] The presence, however, of slightly atypical squamous epithelium in unexpected cervical quarters may lead to confusion in diagnosis and unnecessary radical operations. The protean character of epidermization makes this possibility more real than theoretical. Happily, such errors may be avoided by careful application of the well-known cellular criteria of malignancy and by the knowledge that carcinoma, in contradistinction to epidermization, occurs infrequently in cervical polyps.

In the present series of 117 patients with cervical polyps, two instances (1.7 per cent) of squamous cell *carcinoma* were found. In each, the diagnosis rested not only on the presence of heterotopic epithelium, but also on the atypic characteristics of the malignant cells, namely, hyperchromatism, totally irregular nuclei, and loss of polarity. Summaries of the histories of the two patients with carcinomatous polyps follow:

CASE 1.—(Mount Sinai Hospital, No. 88939.) Mrs. D. B., white secundipara, aged 48 years, was admitted for the sole complaint of slight intermenstrual bleeding of eight months' duration. Examination revealed no gynecologic abnormalities other than the presence of a friable, acorn-sized, endocervical polyp with a wide base. Treatment included cervical amputation, diagnostic curettage, intrauterine application of 2,400 mg. hr. of radium, and three courses of roentgen irradiation to the pelvis during the ensuing eighteen months. Histologic

study of the specimen showed, in addition to epidermization, a localized squamous cell carcinoma at the base of the polyp. The patient has remained perfectly well for six years.

CASE 2.—(Mount Sinai Hospital, No. 73066.) Mrs. R. R., white, quadripara, aged 50 years, was hospitalized because of profuse leucorrhea and slight metrorrhagia of three months' duration. Pelvic examination disclosed the presence of several pea-sized endocervical polyps. Treatment included multiple polypectomy and application of 2,400 mg. hr. of radium to the cervical canal. Microscopic study of the polyps showed some degree of epidermization in all and a squamous cell carcinoma at the tip of one. The patient has also remained perfectly well for six years.

TREATMENT

In the group of 117 patients herein reported, polypectomy was performed in 99 (84.6 per cent) and cervical amputation in the remaining 18 (15.4 per cent). Other surgical procedures for conditions unrelated to cervical polyps were executed in some of the patients (Table V).

TABLE V. SURGICAL MEASURES EMPLOYED, IN ADDITION TO POLYPECTOMY AND CERVICAL AMPUTATION, IN 117 PATIENTS WITH CERVICAL POLYPS

	NUMBER OF PATIENTS	CAUTERIZATION	CURETTAGE		SUBTOTAL HYSTERECTOMY
			WITH RADIUM	WITHOUT RADIUM	
Polypectomy	99	*68	6	39	6
Cervical amputation	18	0	3	15	0
Total	117	68	9	54	6

*This number includes several patients of the curettage and hysterectomy groups and, also, an additional patient who had an oophorectomy for cystadenoma.

Cervical polypectomy may be readily and safely accomplished, as observed in this study, by purposeful torsion of the pedicle or by excision with scissors, scalpel, or wire snare. Whenever possible, in either method, the base of the polyp should be clearly visualized and cauterized with the electric cautery. The latter procedure is a most useful adjunct to polypectomy, because it not only accomplishes hemostasis but also eradicates any infection lurking at the base of the polyp. Cauterization was employed in 68 of the 99 patients (68.6 per cent) who had polypectomies. A temporary but severe flare-up of a supposedly quiescent pelvic inflammation followed the polypectomy and cauterization in one of the 68 patients. This experience serves to stress the fact that unexpected disastrous results occasionally follow even minor cervical procedures when the presence of smoldering salpingitis is not recognized.

Intrauterine curettage, with or without the application of radium, is frequently indicated at the time of polypectomy because abnormal uterine bleeding is, as aforementioned, not always clearly explained by the presence of an innocuous-appearing cervical polyp. This is especially true in women at or just beyond the climacteric, an age when both benign uterine bleeding and carcinoma of the uterine body are most often encountered. Intrauterine application of radium was employed in 9 patients of the present series because the bleeding could not be explained on the basis of polyposis alone.

No physician is justified in assuming on the basis of macroscopic appearance alone, that a cervical polyp is benign. Neither the fact that only 1.7 per cent of such polyps are malignant nor the financial consideration involved in routine histologic studies can ease the "burden of responsibility" from the physician who carelessly discards a cervical polyp. Moreover, the *entire* polyp should be thoroughly examined, since early carcinoma is, as illustrated by the two instances cited previously, a localized process. The mere suspicion of malignancy warrants the use of radium irradiation and demands close scrutiny of the patient's future course.

RECURRENCE

Only 104 of the 117 patients herein reported were successfully followed for periods varying from one to seven years. The follow-up examinations, conducted by the respective operators, did not reveal a single recurrence of cervical polyp in the group of 104 women.

SUMMARY

The clinical and pathologic features of cervical polyps, as encountered in 117 patients, are presented. It is shown that the etiology of a cervical polyp cannot be ascribed to an endocrine disorder and that it is more likely an independent neoplastic process with some relationship to the trauma of childbirth.

The importance of a careful histologic study of removed cervical polyps is emphasized because the tendency to epidermization, or substitution of the columnar epithelium by stratified squamous epithelium, may lead, when misinterpreted, to either overlooking of a squamous cell carcinoma or a useless radical operation.

The histories of two patients (1.7 per cent) who had carcinomatous polyps are related.

The follow-up studies of 104 of the 117 patients indicate the relative infrequency of recurrence of cervical polyps removed either by polypectomy or by cervical amputation.

REFERENCES

(1) *Witherspoon, J. T.:* Clinical Gynecological Pathology, Philadelphia, 1939, Lea & Febiger. (2) *Häggström, P.:* Ztschr. f. Geburtsh. u. Gynäk. **102:** 36, 1932. (3) *Taylor, H. C., Jr.:* Am. J. Obst. & Gynec. **23:** 309, 1932. *Novak, E., and Yui, E.:* Ibid. **32:** 674, 1936. (4) *Fetterman, F. S.:* Ibid. **28:** 120, 1934. (5) *Geiger, C. J.:* Ibid. **32:** 465, 1936. (6) *Israel, S. L., and Mazer, C.:* Ibid. **36:** 445, 1938. (7) *Schroeder, R.:* Lehrbuch der Gynäkologie, Leipzig, 1926, F. C. W. Vogel. (8) *Fluhmann, C. F.:* Northwest Med. **26:** 244, 1927. (9) *Geist, S. H.:* Am. J. Obst. & Gynec. **4:** 30, 1922. (10) *Herrell, W. E., and Broders, A. C.:* Surg. Gynec. Obst. **61:** 751, 1935. (11) *Fluhmann, C. F.:* Am. J. Obst. & Gynec. **15:** 1, 1928. (12) *Meyer, R.:* Zentralbl. f. Gynäk. **47:** 946, 1923. (13) *Teacher, J. H.:* A Manual of Obstetrical and Gynaecological Pathology, London, 1935, Oxford University Press. *Frankl, O., and Ringer, M.:* Zentralbl. f. Gynäk. **56:** 1858, 1932. *Douglass, M., and Faulkner, R. L.:* Essentials of Obstetrical and Gynecological Pathology, St. Louis, 1938, The C. V. Mosby Co.

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Parkes, A. S. and Dodds, E. C.: Interruption of Early Pregnancy by Means of Orally Active Oestrogens, Brit. M. J. **2:** 557, 1938.

Experiments were carried out on the interruption and inhibition of early pregnancy by the oral administration of two new estrogens, ethynyl estradiol and diethylstilbestrol. The former is a derivative of estradiol, the latter, a synthetic substance, not quite as effective. Both of these substances given orally inhibit the effect of progesterone and prevent the implantation of the blastocysts in rabbits. Small doses of the synthetic product prevent implantation in rats, and ethinol estradiol interrupts early pregnancy in rabbits. The application of these substances for similar purposes in women is as yet problematic. Theoretically the results of their administration should be the same, although the period of their effectiveness would be relatively much shorter than in rabbits.

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PREGNANCY AFTER THORACOPLASTY FOR TUBERCULOSIS

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IN A PREVIOUS paper[1] we presented a study of pregnancy, labor, and the puerperium in patients who received collapse therapy for pulmonary tuberculosis at Herman Kiefer Hospital. This investigation was concerned with artificial pneumothorax and phrenic nerve operations, and did not include thoracoplasty. Among 144 women of all ages who received collapse therapy by thoracoplasty operations while on the tuberculosis service of this hospital, we were able to trace the records of 10 who later became pregnant one or more times. In view of the increasing use of this operation, particularly in young women, it was thought that a study of the results in these cases, combined with a review of the literature, should yield information of value not only to the obstetrician, but also to the phthisiologist and the thoracic surgeon.

The production of pulmonary collapse by the extensive operative procedure of thoracoplasty has, as a rule, been confined to those tuberculous patients with advanced lesions who have shown little or no favorable response to more conservative treatment. The results, as reported from this hospital[2] and elsewhere, have been so generally satisfactory as to mark a distinct advance in the treatment of serious tuberculosis. The very fact, however, that such extreme measures were necessary for the control of the pulmonary condition would seem to be sufficient contraindication to the strain of childbearing with its possible effect on the tuberculosis. Moreover, it has been suggested that the restriction of respiratory exchange due to the collapse might prevent proper development of the pregnancy, or perhaps with the extra load of pregnancy and labor might dangerously exceed the cardiac capacity. Jameson,[3] on the basis of 11 case reports in the literature, states, "As far as the risks of childbirth are concerned, it would seem that one should fear the possibilities of respiratory embarrassment during labor more than the likelihood of the tuberculosis being reactivated."

In addition to those cited by Jameson, we have found the following reports in the literature.

Alberts[4]: A 25-year-old primigravida who had had unilateral tuberculosis for five years when a thoracoplasty was done. She was delivered eleven months later, after a one-and-one-half-hour labor, of a 7-pound child. She had done heavy work during pregnancy, and had received no special care. She nursed her baby for fifteen months, and at the end of that time there was no activity on the affected side or extension to the other.

Vannucci[5]: A 21-year-old patient in 1928 was found to have tuberculosis of the upper one-third of the right lung, and a small area at the left apex. Thoracoplasty operations were done on the right side in February and September, 1930. She was delivered in January, 1933 of a normal child which was breast fed. During pregnancy there was a loss in weight of 5 kilograms. X-rays in September, 1933 showed no definite ill effect on the pulmonary condition.

Amorin[6]: A 21-year-old woman with ulcerofibrotic involvement of the whole left lung became pregnant while improving under treatment. Thoracoplasty was done in two stages, at the second and sixth months, with no postoperative trouble. Delivery of a 2,700 gm. child occurred at term. The child did well on mixed breast and artificial feeding. During pregnancy there was continued improvement. Amorin believed the results in this case to be a potent argument against therapeutic abortion for tuberculosis. He found only two previous reports of thoracoplasty during pregnancy, namely, those of Sayé in 1924, and Rist in 1926.

Boquist, Simons, and Myers[7]: After seven years of treatment for tuberculosis, including a two-stage thoracoplasty done in May, 1922 and September, 1923, the patient was discharged from the hospital in March, 1924. She was delivered in March, 1929 by midforceps operation after a four-hour-and-twenty-minute labor. The baby was normal, and the puerperium uneventful. In the last month of pregnancy there was considerable dyspnea, and during labor this became extreme with pulse rate up to 130 or 140 per minute. With active care of the baby and housework there was reactivation of the disease a little less than a year after delivery, which required sanatorium care for a year.

Blisnjanskaja and Lasarevitch[8]: Reported the case histories of 7 women who had become pregnant following thoracoplasty which had been done after other collapse therapy had failed to control advanced tuberculosis.

1. Delivery four years after thoracoplasty. The child was premature, weighing 1,800 gm., but lived. The mother was well six years later when an abortion was induced.

2. Term delivery of a 3,600 gm. child two years and two months after thoracoplasty. There was no marked reactivation of the disease until two years after pregnancy when there was exacerbation with hemoptysis.

3. Low forceps delivery of a 3,500 gm. child three and one-half years after a thoracoplasty operation. The patient was working when hemoptysis occurred one year and five months after delivery.

4. The first child was born fifteen months following thoracoplasty. Some exacerbation of the disease occurred. During the second pregnancy (five years after thoracoplasty) there was hemoptysis at seven months. The child weighed 3,200 gm. Reactivation of the tuberculosis occurring nine months after delivery was ascribed to "arduous circumstances" rather than pregnancy.

5. Two years after thoracoplasty, therapeutic abortion was done because of reactivation of the tuberculosis. A year later the patient was delivered by low forceps of a 2,500 gm. child. There was again reactivation of the disease, but the patient was doing well eighteen months after delivery.

6. Delivery of a child weighing 3,700 gm. about two years after thoracoplasty operation. The patient was in good condition eighteen months later. An abortion occurred several years later.

7. Six months after thoracoplasty a therapeutic abortion had been done. Two years later, the patient had had a spontaneous premature labor at thirty-six weeks which followed a fall from a chair. The child died the second day. Five months post partum there was no evidence of reactivation.

From their experience, these authors conclude that when thoracoplasty gives good results, pregnancy may be allowed if living conditions are good. On the contrary, if the tuberculosis is subcompensated for by the operation, pregnancy should be interrupted. Delivery should be operative in the second stage of labor to avoid the strain of expulsive efforts.

Guillemin and Chabeaux:[9] The 22-year-old woman in her second pregnancy had previously been treated satisfactorily by phrenicectomy. The last menstrual period began on March 11, 1936. Examination in July showed the pulmonary condition worse. A three-stage thoracoplasty done in August was without complications. She was delivered Dec. 19, 1936, of a rather small child. A year after delivery the patient was in good health and gaining weight while active in her housekeeping.

Table I gives the salient features in our 10 cases. It will be noted that the first two patients had interruption of the pregnancy in the early months. Both were treated at other hospitals. The first was apparently an instance of curettage for incomplete abortion. In the second case it is uncertain whether or not reactivation of the tuberculosis was the indication for therapeutic abortion. Although several of the remaining 8 patients were not delivered at this hospital, sufficient data for our investigation were obtainable.

Our 8 cases in which pregnancy was allowed to proceed plus those reviewed by Jameson[3] and those from the literature, abstracted by us, make a group of 31 patients for study. The possible ill effects of pregnancy on the mothers should be indicated by the number who died or whose tuberculosis became worse during pregnancy or during a period of one year after delivery. It will be noted that some patients in the group were not observed for a full year post partum. However, this number was too small to affect the conclusions which may be drawn from Table II.

Table II shows that 6 out of 31, or about one out of five, patients with thoracoplasty for tuberculosis who became pregnant had serious exacerbation. It is recognized that patients with advanced tuberculosis (even though it be arrested) may have reactivation of the disease. However, reactivation in these cases seemed to bear a relationship to childbearing. A possible exception is our patient who died, since in addition to active involvement of the other lung and tuberculous pneumonia, she had amyloid disease of the kidneys which may well have antedated the pregnancy. The other 5 patients with exacerbations responded to treatment after delivery.

It is interesting that two of our patients went through a second pregnancy without trouble in either. A patient reported by Blisnjanskaja and Lasarevitch was not so fortunate. She had two full-term pregnancies with exacerbations during each. Another, after a therapeutic abortion because of reactivation of the disease, had a child five years after thoracoplasty with hemoptysis during pregnancy and definite exacerbation nine months following delivery.

It is also of considerable interest that thoracoplasty has been successfully performed during pregnancy in at least four instances (Sayé, Rist, Amorin, and Guillemin and Chabeaux). It would seem from this that the procedure might be seriously considered for those few pregnant tuberculous patients who do unsatisfactorily even with artificial pneumothorax or phrenic nerve operation.

In regard to the accuracy of the statistics shown in Table II, it may be of significance to note that 4 of the 6 cases with unfavorable results occurred in the two series (15 altogether) reported by Blisnjanskaja and Lasarevitch and by us, or 2 out of 7 and 2 out of 8 cases, respectively. This apparent discrepancy in results may be due to the small numbers of cases involved, though the possibility exists that the tendency in single case reports has been toward publishing only the good results. If the latter is the case, the expectation of unfavorable outcome for these patients should be considerably greater than indicated in Table II.

TABLE I. HERMAN KIEFER HOSPITAL CASES OF PREGNANCY AFTER THORACOPLASTY

AGE, RACE, PARITY	THORACOPLASTY	DELIVERY OR ABORTION	DURATION OF PREGNANCY	SPONTANEOUS OR OPERATIVE	CHILD	TUBERCULOSIS IN PREGNANCY	COMPLICATIONS IN PREGNANCY AND LABOR	CONDITION AFTER DELIVERY
I. B. Age 22 White Grav. iv	April and June, 1933	July 13, 1934	10 wk.	Operat. abortion (no fetus)	--	No change?	None	August, 1938. Working, tuberculosis arrested
V. Mc. Age 29 White Grav. ii	Feb. and March, 1932	Jan., 1936	8 to 12 wk.	Operat. abortion	--	No change?	Weakness, nausea	Sept., 1938. Weak, losing weight
M. W. Age 26 White Grav. i	Feb. and March, 1934	July 6, 1936	20 wk.	Spont.	1 lb. Macerated	Active on other side Tuberculous pneumonia	Amyloid kidneys Uremia	Died 5 days post partum
R. F. Age 22 White Grav. i	Feb. and March, 1934	Jan. 19, 1936	34 wk.	Spont.	4 lb. 6 oz. Died 16 days	No Change	None	April, 1937. Marked tuberculosis of other side
E. S. Age 29 White Grav. ii-iii	March and May, 1933	June, 1935 Feb., 1937	Term 2 to 3 mo.	Spont. Spont.	6 lb. 12 oz. Well	No change	None	June, 1938. No progression. Active at home
L. M. Age 30 Negro Grav. vi	June to Sept., 1932	Aug. 21, 1935	Term	Spont.	6 lb. 7 oz.	No change	None	Dec., 1937. No progression. Feels well
E. P. Age 26 Negro Grav. vi	May, 1933, to July, 1935	Dec. 18, 1937	Term	Spont.	5 plus lb. Well	No change	None	July, 1938. Afebrile, sputum neg.
L. H. Age 16 White Grav. i-ii	Feb. and June, 1930	March, 1936 Oct., 1937	Term Term	Spont. Spont.	5 lb. 10 oz. 6 lb. 12 oz. Both well	No change No change	Bronchitis Dyspnea None	Sept., 1938. Well, active at home
J. L. Age 30 White Grav. vi-vii	Oct. to Dec., 1930	Feb., 1933 March, 1935	Term Term	Spont. Spont.	7 lb. 8 oz. 6¼ lb. Both well	No change Same	None None	Oct., 1938. Well after both pregnancies
H. H. Age 26 White Grav. i	Feb. to April, 1933	June, 1935	Term	Low forceps	8 lb. 9 oz.	No change	None	August, 1938. 5 months preg. No progression

Fears as to the dangers from respiratory difficulty during pregnancy and labor are not borne out by the records in these cases. The 31 women had a total of 34 pregnancies which were prolonged to at least five months. In only 3 instances was mention made of dyspnea during pregnancy or labor. With our patient this was present only during pregnancy and was not troublesome. Dyspnea was considerable, however, in the cases reported by Mueller and by Boquist, Simons, and Myers.

TABLE II. MATERNAL RESULTS FOR PATIENTS WHO HAD THORACOPLASTY AND ONE OR MORE PREGNANCIES

(Showing the deaths and the number whose tuberculosis became worse during pregnancy or in the year after delivery)

UNAFFECTED	WORSE DURING PREGNANCY	WORSE POST PARTUM	DIED	TOTAL
25	1	4	1	31

Moreover, in the latter case the dyspnea reached a serious degree during labor. We have found no record of induction of premature labor because of dyspnea, intractable vomiting, or other complication due to thoracoplasty.

The possible effect of thoracoplasty on the outcome of pregnancy is of importance. In the 34 pregnancies occurring among these 31 women there were 5 spontaneous premature labors or late abortions. This rather high incidence approximated that found by us[1] among the tuberculous patients of our previous investigation—regardless of whether or not they had received collapse therapy or other treatment, or no treatment at all. Consequently, the excess of the rate over that for the nontuberculous patients in this hospital seemed attributable to the tuberculosis itself. With the patients having thoracoplasty, it also appears possible that the disease rather than the consequences of the operation was responsible for at least some of the premature interruptions. Although Blisnjanskaja and Lasarevitch believed that the cause in one of their cases was a fall from a chair, our two instances occurred in the only patients showing exacerbation of the tuberculosis. There was no evident explanation for the other two cases found in the literature. The only fetal or neonatal deaths reported for these 34 pregnancies were the 3 which occurred among the 5 children born prematurely.

DISCUSSION

During recent years the necessity for therapeutic abortion for various medical conditions has been decreasing as therapeusis for the conditions requiring it has improved. We refer particularly to pregnancy complicated by such conditions as pernicious vomiting, toxic thyroid, heart disease, diabetes, and the milder arrested forms of pulmonary tuberculosis. In accord with this tendency it seems possible that therapeutic abortion can also be resorted to less frequently in other forms of tuberculosis, even in cases so far advanced as to require thoracoplasty for control. With the increasing use of this procedure, the problem of whether or not to allow a woman so treated to continue with her pregnancy will appear more frequently.

So far as we have been able to ascertain, actual experience with this situation has been very limited up to the present. An examination of the medical literature has revealed only one small series of 7 cases and scattered cases to the number of 16 (with data sufficient to be of value). These with 8 cases reported herewith, make a group of 31 for study.

The 31 women had 34 full-term or premature deliveries. One mother died and 5 others had serious exacerbation of the tuberculosis during pregnancy or within one year after delivery. As explained before, we doubt that these figures show quite the true expectation for trouble. They probably do indicate, however, that the majority of women may safely go through pregnancy after thoracoplasty. Nevertheless, risks for some are definitely greater than admitted by the more optimistic.

Complicating respiratory difficulty was mentioned in three cases, though this was serious (not fatal) in but one. Two patients went through 2 full-term pregnancies safely, though a third woman had exacerbations in both.

It is noteworthy that thoracoplasty has been done successfully during pregnancy in at least four instances.

We found no definite evidence that thoracoplasty had deleterious effects on pregnancy. There was a rather high incidence of premature labors, but this was in accord with our previous findings in tuberculous women regardless of the type of treatment. The 3 fetal deaths in this group occurred among premature babies.

We are indebted to the members of the Departments of Tuberculosis and Thoracic Surgery for many helpful suggestions in the preparation of this paper.

REFERENCES

(1) *Seeley, W. F., Siddall, R. S., and Balzer, W. J.:* Am. J. Obst. & Gynec. **37:** 741, 1939. (2) *O'Brien, E. J.:* J. Thoracic Surg. **3:** 159, 1933. *O'Brien, E. J., Tuttle, W. M., Day, J. C., and O'Connor, J. P.:* Ibid. **8:** 1, 1938. (3) *Jameson, E. M.:* Gynecological and Obstetrical Tuberculosis, Philadelphia, 1935, Lea & Febiger. (4) *Alberts, L.:* Med. Welt **62:** 1137, 1932. (5) *Vannucci, G. C.:* Gazz. internaz. med.-chir. **44:** 15, 1934. (6) *Amorin, A.:* Rev. de Phtisiol. **15:** 461, 1934. (7) *Boquist, H. S., Simons, J. H., and Myers, J. A.:* Am. Rev. Tuberc. **31:** 48, 1935. (8) *Blisnjanskaja, A. I., and Lasarevitch, A. I.:* Gynéc. et obst. **34:** 207, 1936. (9) *Guillemin, A., and Chabeaux:* Red. méd. de Nancy **65:** 30, 1937.

A COMPARATIVE STUDY OF MALE AND FEMALE PELVES*

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In a recent communication[1] we reported the results of a roentgenologic study of the size and shape of the pelvic inlet in 582 primigravid white (clinic) women, 104 nulliparous student nurses from a somewhat different racial stock and a more privileged economic class, and 107 young girls who ranged in age from 5 to 15 years. The pelves of this group were classified according to the Thoms' system of classification, which is based on the relative lengths of the transverse and anteroposterior diameters of the pelvic inlet as follows:

Dolichopellic or Anthropoid Type: The transverse diameter is less than the anteroposterior diameter.

Mesatipellic or Round Type: The transverse diameter either equals the anteroposterior diameter or exceeds it by no more than 1 cm.

*This investigation was aided by grants from the Fluid Research and Teaching Funds of Yale University School of Medicine and the General Education Board of the Rockefeller Foundation. Dr. Hugh M. Wilson, Associate Professor of Radiology, Yale School of Medicine, kindly made available to us the necessary radiologic facilities for this study.

Brachypellic or Oval Type: The transverse diameter exceeds the anteroposterior by from 1.1 to 2.9 cm.

Platypellic or Flat Type: The transverse diameter exceeds the anteroposterior by 3 cm. or more.

This classification we have used in clinical practice during the past four years, and it appears to be of greater usefulness and of more ready comprehension than any other classification with which we are familiar. Nevertheless, for certain comparisons a classification based upon the pelvic index, as suggested by Turner,[2] is also of usefulness, as will be noted later.

The incidence of the various types of pelves in these 686 adult white women is shown in Table I.

TABLE I

TYPE	582 CLINIC WOMEN PER CENT	104 STUDENT NURSES PER CENT	TOTAL 686 ADULT PER CENT
Dolichopellic	15.0	37.5	18.4
Mesatipellic	44.8	44.2	44.7
Brachypellic	34.3	18.2	31.8
Platypellic	5.6	--	4.7

These findings are of considerable interest if we compare them with what is described as the "normal" female pelvis in textbooks of anatomy. In such texts we find the normal female pelvis described as one in which the transverse diameter of the inlet exceeds the anteroposterior diameter by more than 2 cm. On the basis of this criterion we find that only 14.9 per cent of the clinic women and 5.7 per cent of the student nurses possess this type of pelvis. Obviously the prevailing concept of the "normal" pelvis of white women needs revision, a matter which we have previously discussed.[3]

In order to be adequate for clinical purposes a survey of the pelvis cannot be limited to a study of the inlet alone, but it must include a description of the remainder of the pelvis as well. During the past year, using improved techniques, we have made such a survey of 200 white women. It is our opinion that not only is the shape of the various segments of the pelvis of importance but that certain diameters are equally important. These diameters are:

Pelvic Inlet
1. Anteroposterior diameter
2. Transverse diameter
3. Posterior sagittal diameter

Midpelvic Plane
1. Anteroposterior diameter
2. Transverse diameter (interspinous)
3. Posterior sagittal diameter

Pelvic Outlet
1. Transverse diameter
2. Posterior sagittal diameter (intertuberal)

For a further discussion of these diameters and the points from which they are estimated, the reader is referred to a recent communication by one of us.[4]

In the present paper we wish to report the results of an x-ray study of the pelves of 69 white adult male students, a group which resemble very closely the student nurses of our previous series both in economic level and in national derivation. Such a survey has a distinct clinical interest due to the fact that certain features regarded as characteristically male may occur in female pelves, a fact which has been known for many years and which has recently been emphasized by Caldwell and Moloy.[5] Such occurrences may have pronounced obstetric importance, and may be the cause of severe dystocia.

In the first consideration of this survey of the male pelvis, we would call attention to the description of the "normal" male pelvis as found in anatomic texts. In general the male pelvic inlet is said to be heart-shaped and to have an anteroposterior diameter which is smaller than its transverse. A comparative study of our findings may be stated in terms of the pelvic index (P.I. $= \frac{\text{A.P.} \times 100}{\text{Trans.}}$).

The average pelvic index of our group was 100.5. This is considerably higher than the index of 80.8, the average reported for European males, by Turner (77.0), Verneau (80.0), Topinard (80.0), and Krause (84.4), whose figures are still cited as typical of white males in modern textbooks of anatomy. Only two of the 69 men in our series had a pelvic index of less than 85 (77.0 and 84.8).

According to the Thoms' classification, the occurrence of pelvic type in the group was as follows:

Dolichopellic type	20 instances or 28.9%
Mesatipellic type	34 instances or 49.2%
Brachypellic type	15 instances or 21.7%

Thus, it is seen that in male pelves, as in female pelves, these basic pelvic types appear. In this limited series the percentage ratio is not greatly unlike that of the student nurse group given above.

The various average pelvic diameters observed in the 69 males and the 200 females of our present series are listed in Tables II and III, in which cases are arranged according to pelvic type.

TABLE II. MEAN VALUES FOR PELVIC TYPES IN 200 WHITE WOMEN

TYPE	INLET			MIDPLANE			OUTLET	
	A. P.	TRANS.	P. S.	A. P.	TRANS.	P. S.	TRANS.	P. S.
Dolichopellic	12.50	11.72	5.07	12.55	9.45	5.22	8.95	7.84
Mesatipellic	11.75	12.32	4.48	12.34	10.34	5.23	9.16	7.71
Brachypellic	11.06	12.67	4.15	12.01	10.32	5.23	8.92	8.05
Platypellic	9.0	12.67	2.75	11.67	10.45	4.71	9.12	7.58

TABLE III. MEAN VALUES FOR PELVIC TYPES IN 69 WHITE MALES

TYPE	INLET			MIDPLANE			OUTLET	
	A. P.	TRANS.	P. S.	A. P.	TRANS.	P. S.	TRANS.	P. S.
Dolichopellic	12.30	11.60	4.89	12.43	8.54	4.47	10.65	7.68
Mesatipellic	11.46	11.87	4.01	12.07	8.66	4.22	10.75	7.49
Brachypellic	10.77	12.01	3.63	11.96	8.86	4.33	10.72	6.97

The above figures show that in each pelvic type the male pelvis has a smaller capacity than that of the female. The diameters which designate the chief differences are the bispinous and the three posterior sagittals. The male pelvic inlet as it occurred in our series is not

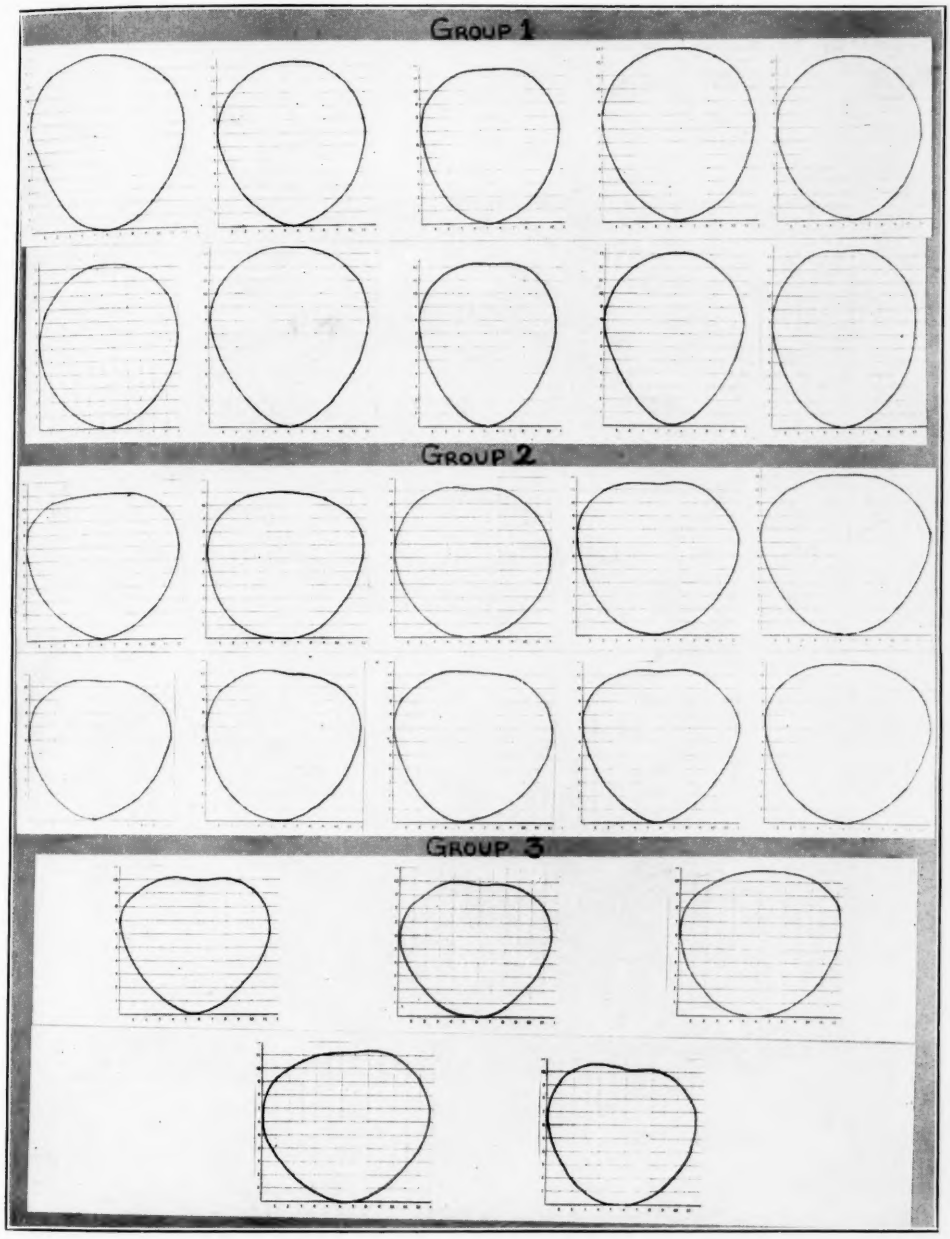

Fig. 1.—Group I, representative tracings of pelvic inlets of the dolichopellic or anthropoid group. Group II, representative tracings of pelvic inlets of the mesatipellic or round group. Group III, representative tracings of pelvic inlets of the brachypellic or oval group.

greatly different from that of the female. The term "heart-shaped" would be a very inappropriate designation for the inlet of the great majority of these male pelves. This is evident from the tracings of the inlet of representative pelves shown in Fig. 1. Attention also is directed especially to the forepart of the pelvic inlet. As will be seen in most instances, this is not angular but a sweeping curve and is not greatly unlike that seen in most female pelves. The relative shortening of the posterior sagittal diameter of the inlet, which is said to be so characteristic of the male pelvis, is not marked in our series, an average of approximately 0.5 cm. less than the figures for the female series.

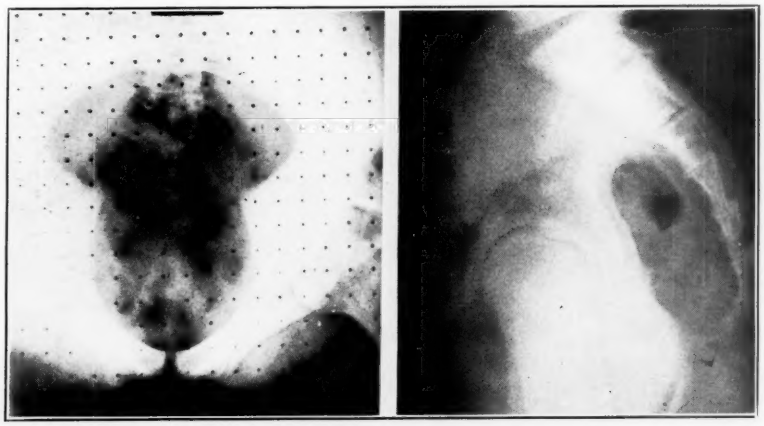

Fig. 2.—Dolichopellic or anthropoid type of male pelvis. Lateral view shows typical male notch, and the sacrum is composed of six segments.

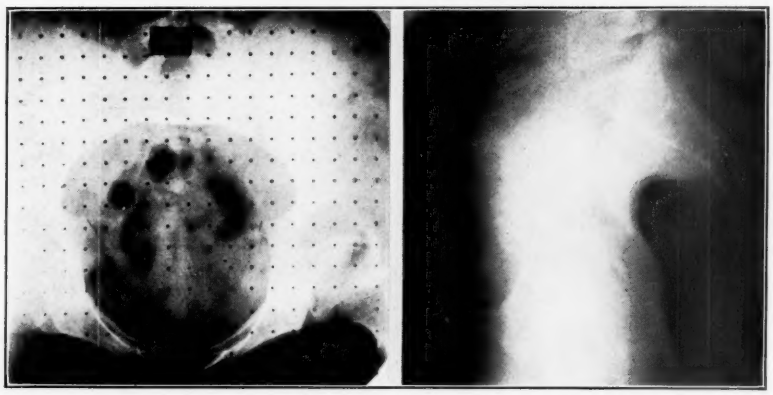

Fig. 3.—Mesatipellic or round type of male pelvis.

The most typical male characteristics in pelvic contour in our series were the shape of the sacrosciatic notch and the angle formed by the pubic rami. The sacrosciatic notches showed typical male features in all subjects examined, although in a few cases a wideness was present to the extent that the female type was suggested. The subpubic angle was not studied roentgenologically in all cases, but in those in

which this was done it was found to be typically masculine. A word should be added concerning the bituberal or outlet transverse diameters given above. In the women this diameter was determined by palpation, but in the male series it was determined by x-ray. The findings show clearly the result of the lack of uniformity in designating that part of the tubera ischii from which measurements should be taken and suggest studies to correct this error. Because of these discrepancies the intertuberal diameters of the two groups are not comparable.

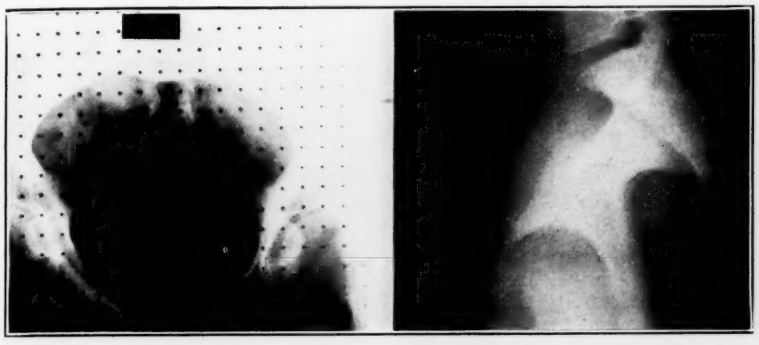

Fig. 4.—Brachypellic or oval type of male pelvis.

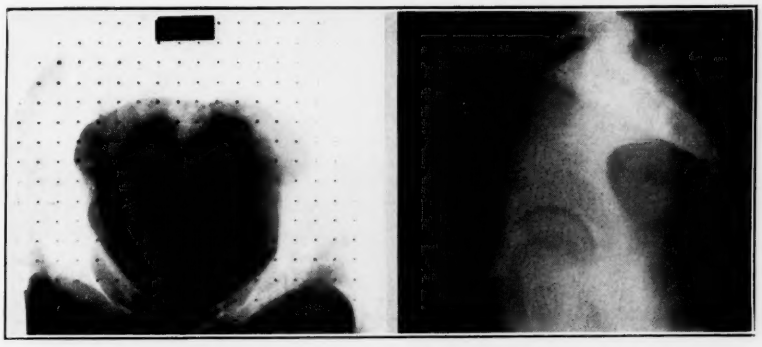

Fig. 5.—The pelvis inlet shows a tendency to the "heart-shape." The sacrum in its lateral aspect shows changes suggestive of rachitic influence.

A study of the sacrum in this series as seen in its lateral aspect revealed the presence of six segments in 9 instances (so-called high assimilation). These were equally divided in the three types, although in our opinion this variation is more often seen in association with the dolichopellic type pelvis in women.

A study of the curve of the anterior sacral surface from above downward showed the usual deviations from a normal sweeping curve, which we also noted in our female series. In seven instances the upper two-thirds of the anterior sacral surface showed a lack of the usual concavity with the exaggeration of the forward curve of the lower one-third of this surface. In two instances the entire anterior surface

of the sacrum was straight or convex in its lateral outline from above downward, and the inlet in these cases showed a definite tendency to the heart-shaped form with relatively shortened posterior sagittal diameters (3.3-3.3), Fig. 5. These sacral findings strongly suggest to us changes due to rachitic influence.

We may summarize our findings in this comparative study of male and female pelves as follows:

1. The pelvic bones in males are heavier than those found in females, and in general the whole pelvis of the former has a more angular appearance.

2. The pelvic inlet in males appears in general more circular, and the posterior sagittal diameter in this plane is slightly shorter than that seen in female pelves. This is due to a slight displacement posteriorly of the widest transverse diameter. The forepart of the pelvic inlet differs but slightly from that seen in female pelves and the so-called "heart-shaped" pelvic inlet was not characteristic of the great majority of pelves in our series.

3. The constant characters seen in male pelves were the structural heaviness and prominence of the ischial spines with narrowing of the pelvic side walls from above downward, the angular pelvic arch with a relatively narrow subpubic angle and the type of sacrosciatic notch which has been described as characteristically male.

4. The three main pelvic types which we have found in female pelves, i.e., dolichopellic, mesatipellic, and brachypellic, were also found to occur in male pelves.

REFERENCES

(1) *Greulich, W. W., and Thoms, H.:* Trans. N. Y. Acad. Sc. **1:** 12, 1938. (2) *Turner, W.:* J. Anat. & Physiol. **20:** 125, 1886. (3) *Greulich, W. W., Thoms, H., and Twaddle, R. C.:* J. A. M. A. **112:** 485, 1939. (4) *Thoms, H., and Wilson, H. M.:* Yale J. Biol. Med. **11:** 179, 1939. (5) *Caldwell, W. E., and Moloy, H. C.:* AM. J. OBST. & GYNEC. **26:** 479, 1933.

Jackson, Ed.: Prophylaxis for Ophthalmia Neonatorum, Am. J. Ophth. **21:** 438, 1938.

The prevention of ophthalmia neonatorum due to the gonococcus has been very widely provided for in laws and regulations of health departments. The instillation of silver nitrate solution at the time of birth has been most generally prescribed. Silver nitrate is a severe irritant to the conjunctiva and cornea and cases have occurred in which it has caused serious conjunctivitis when no gonococcal infection was present. Its use at too short intervals, more than one application in twenty-four hours, has also caused permanent opacities of the cornea.

Jackson feels that the more recent introduction of silver acetate as a safer and more widely efficient prophylactic should be welcomed by the profession. It would be particularly useful in sparsely settled districts where frequent renewal of the silver nitrate solution cannot be obtained without delay.

J. P. GREENHILL.

AN INFANT INCUBATOR

Employing Controlled Mixtures of Helium and Oxygen to Combat Respiratory Failure

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UP TO the year 1938 many infants of diabetic mothers had experienced respiratory failure immediately after birth, the exact cause of which at that time seemed obscure but now appears to be related to a disturbed hormone balance. Prior to this knowledge it was suggested by one of us (P. W.) that helium-oxygen therapy might be of aid to such infants. For this purpose the incubator here described was constructed. The objectives of this incubator are to maintain the infant at the proper temperature and in an atmosphere containing only oxygen and helium. According to Alvan L. Barach,[1] to whom we are indebted for helpful suggestions and advice, a mixture of 20 per cent oxygen and 80 per cent helium has a measurably lighter density than room air and hence should require less effort in breathing on the part of the infant. Thus the aid to respiration is a mechanical one. Other investigators[2] have also reported beneficial effects of breathing helium-oxygen mixtures when respiration is embarrassed. Since the use of this chamber was started, the respiratory failure of newborn infants of diabetic mothers has been successfully prevented by prenatal hormone therapy. However, during the three years that this apparatus has been in use, a number of infants have been aided by being placed in the incubator, and the use of the equipment with other gaseous mixtures than the one originally proposed has proved helpful in some cases. In addition to its special feature of making it possible to determine and maintain the composition of the gaseous mixture in the chamber, this apparatus incorporates the four basic requirements of an incubator, namely, maintenance of proper temperature, maintenance of proper ventilation or oxygenation, maintenance of adequate humidity, and easy access to the infant without harmful exposure.

CONSTRUCTION OF APPARATUS*

The chamber (Figs. 1 and 2) is made of galvanized sheet iron, its inside measurements being 56 by 30.5 by 23 cm. and its volume, 39.3 liters. The cover, which has a large plate glass window, fits into a water seal, making the chamber air-tight. A pipe at the top, *D* (Fig. 2) and another, *A*, at the diagonally opposite, lower corner facilitate thorough ventilation of the chamber and complete evacuation of the air in the chamber when it is to be filled with a gaseous mixture other than room air. The lower pipe has a metal screen in front of it, which prevents any obstruction of this pipe by bed clothing or pillows. The cover is held in place by two stout rubber bands, fastened securely on one side, drawn across the cover, and attached to snap hooks on the other side. The cover can be removed in two or three seconds by snapping up the hooks, throwing a lever operating a quick-throw release valve, *S*, which opens the chamber to the room, and lifting the cover by the two handles on its top. The chamber itself serves as a bassinet. The mattress is formed by inflating air pillows, which are placed in the bottom. By suitable combination these may

*The construction of the chamber and the assembly of the apparatus were the work of V. Coropatchinsky of the Nutrition Laboratory.

be arranged as desired, to produce the proper tilt of the infant. The chamber is insulated on all sides by asbestos board, to prevent rapid changes of temperature. Heat is obtained from four 60-watt bulbs of the bung-hole type (*W-I* to *W-IV*), situated about 50 mm. below the bottom of the chamber. A piece of sheet metal halfway between them and the chamber aids in uniform distribution of the heat. The arrangement of the lamps is indicated in Fig. 2. The middle lamps are controlled by the thermostat, *U*, which maintains the temperature constant within 3° F. The two additional lamps permit rapid heating at the start or whenever, for any reason, it is desired to increase the temperature rapidly. Under ordinary conditions the thermostat adequately maintains the desired temperature. To indicate what the temperature conditions are, a thermometer, *T*, is located inside the chamber,

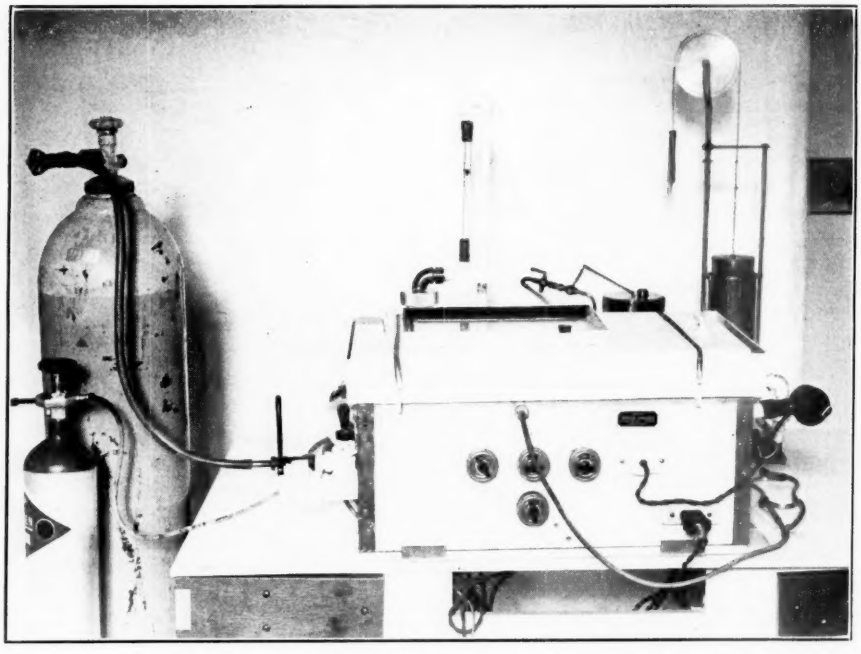

Fig. 1.—Incubator and respiration apparatus for continuous administration of a helium-oxygen mixture to infants.

being suspended from the cover. To insure that the heat transmitted through the bottom of the chamber does not become excessive, a brass tube closed at the end has been soldered into the side of the chamber. This tube fits into a fold in the rubber pillow and thus is not in the way. A thermometer, *TT*, which can easily be withdrawn a sufficient length to be read, is inserted in this tube.

The ventilation system, which is on the closed-circuit principle, consists of a centrifugal type, nonpositive blower,* *B*, a soda-lime container, *C*, a flow meter, *R*, and necessary pipe connecting with the chamber. Flexible metal pipe was used for making the connections to the various instruments, as it was thought that rubber tubing might permit helium to escape by diffusion. Tests of one hour's duration, made since the construction of the apparatus, have indicated that rubber tubing will apparently hold helium satisfactorily. Provision for contraction and expansion of the air in the chamber is made through either the automatic filling device, *E*, or the calibrated, 1-liter spirometer, *K*, which is also used for testing the composition of the gaseous mixture. The carbon dioxide produced by the infant is absorbed from

*Manufactured by Warren E. Collins, Inc., Boston, Massachusetts.

the ventilating air current by Wilson soda-lime, which also serves to maintain a high moisture content of the air. The capacity of the soda-lime container is approximately 3 liters, which is sufficient to remove the carbon dioxide produced by a new-born infant during 72 hours. The flow meter or "rotamesser" gives visual indication of the rate at which the air is being circulated through the chamber and is also used when the system is being filled with a gaseous mixture. The ventilation is usually maintained at 10 liters per minute.

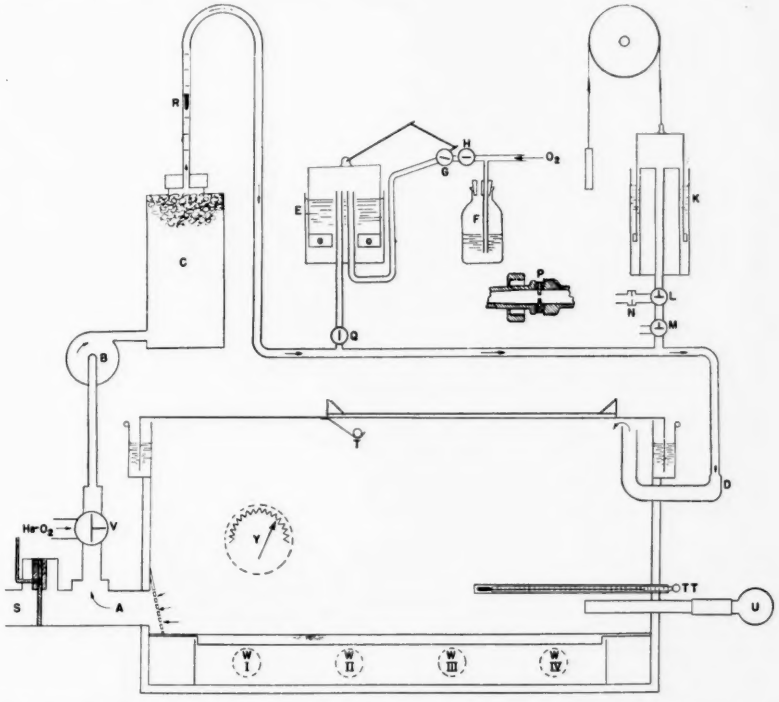

Fig. 2.—Schematic outline of incubator and respiration apparatus for continuous administration of a helium-oxygen mixture to infants. *A*, pipe for outcoming chamber air; *B*, rotary blower; *C*, container for soda-lime; *D*, pipe for ingoing chamber air; *W-I* to *W-IV*, electrical heating units; *U*, thermostat; *T* and *TT*, thermometers; *Y*, rheostat controlling speed of blower; *S*, release valve; *V*, valve for introduction of helium-oxygen mixture; *R*, flow meter indicating rate of flow of gas through ventilation circuit; *E*, automatic gas regulator acting also as expansion chamber; *o*, *o*, cork to compensate for weight of regulator bell; *F*, pressure-regulating bottle; *G*, valve through which oxygen enters regulator; *H*, valve used to disconnect gas regulator from oxygen supply; *K*, densimometer (1-liter spirometer) to determine composition of gaseous mixture in chamber; *L*, valve connecting densimometer with main ventilating air current or with orifice in disk *N*; *P*, enlargement of disk *N*; *M*, valve to connect densimometer with main ventilating air current or to connect a cylinder of gas with the densimometer or the chamber, as desired; *Q*, valve to close gas regulator *E* to main circuit.

Method of Filling With Oxygen-Helium Mixture.—It is desirable to replace the room air present at the start in the system and chamber as completely as possible with the helium-oxygen mixture, because any nitrogen in the chamber air will increase the density of the gaseous mixture and this in turn will necessitate more effort by the infant's lungs in breathing. This is effected by introducing at the inlet to valve *V* (which has been closed to pipe *A* and opened toward blower *B*) a mixture of 75 per cent helium and 25 per cent oxygen from a cylinder.* With the

*As mixtures of 75 per cent helium and 25 per cent oxygen can be obtained in 200 cu. ft. cylinders from the Ohio Chemical and Manufacturing Company, Cleveland, Ohio, this mixture is now used instead of the mixture of 80 per cent helium and 20 per cent oxygen employed in the preliminary studies.

valve *S* open and the valves *Q* and *M* closed to the ventilation system, the oxygen-helium mixture can be introduced first through the blower, soda-lime container, and connecting pipes and then into the top of the chamber through pipe *D*. As this mixture has a density considerably less than room air, it will stratify across the top of the chamber, if admitted at the proper rate, and (by displacement) will force the air in the chamber out through the openings *A* and *S* at the bottom. If the mixture is admitted at the rate of 20 liters per minute for 6 minutes, the air originally in

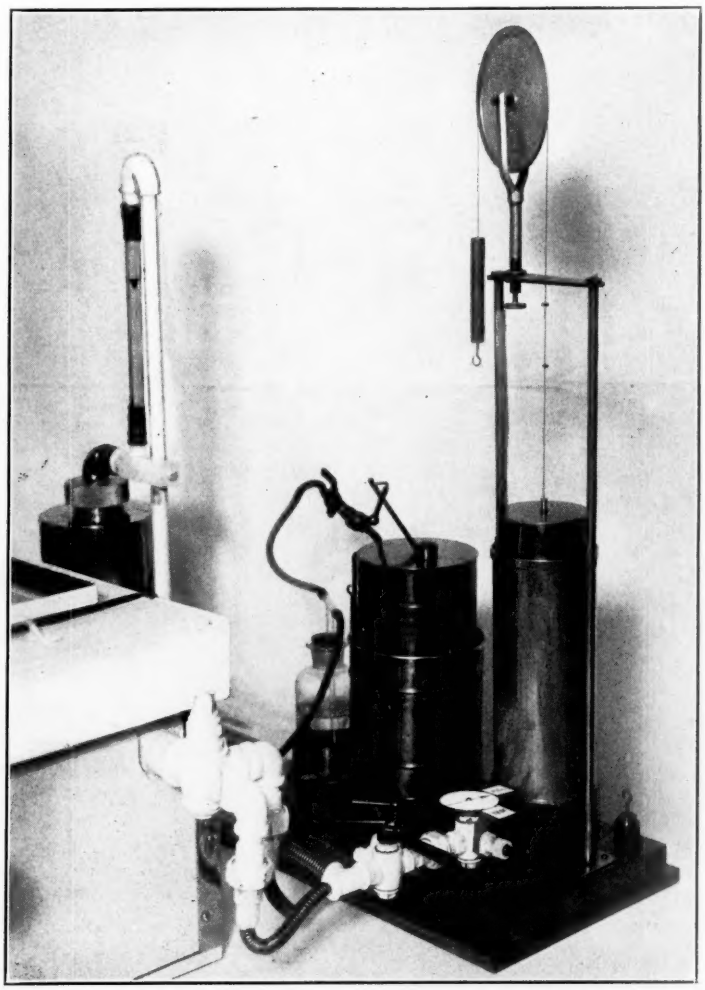

Fig. 3.—Densimometer and gas regulator of respiration apparatus for continuous administration of helium-oxygen mixture to infants.

the chamber will be completely swept out and the system will be filled with the desired mixture. By shutting valve *H* during the early part of the filling and by opening valve *Q* to connect with regulator *E* and valves *M* and *L* to connect with spirometer *K*, the reservoirs of the units *E* and *K* can by manual manipulation be washed out with the oxygen-helium mixture and then partially filled with this mixture. This is done to prevent the introduction into the system of gases other than the desired mixture. This extra gas replaces gas used in testing the composition of the mixture.

Method of Analysis of Gaseous Content of Chamber.—It is important to know that the gaseous mixture inside the chamber is composed of the desired percentages of helium and oxygen and that this composition remains constant during the use of the equipment. It is also necessary to know that the infant has sufficient oxygen at all times. Therefore a simple method for determining the composition of the gaseous mixture was needed. For this purpose a densimometer (Fig. 3 and *K*, Fig. 2) was designed, based upon the principle that, because of the difference in density of helium and oxygen, the rate of effusion of a mixture of these gases will vary according to the composition of the mixture. The densimometer consists of a 1-liter spirometer, the bell of which (originally exactly counterpoised) is overweighted by a 100 gm. brass ring. The spirometer is sealed with mineral oil.* Provision is made for passage of the gas from the spirometer through an orifice in the disk *N*. This disk (enlargement *P*, Fig. 2) is of brass, 0.8 mm. thick, in which an orifice 0.23 mm. in diameter has been made with a No. 80 drill. Even with great care the size of the orifice produced by the No. 80 drill will not be uniform in all cases. A number of disks with these orifices were made and tested. After a standard time for passage of a given quantity of gas had been established, the orifices of the disks that required longer than the standard time for the passage of gas were enlarged by reaming with a needle. Disks with orifices permitting too

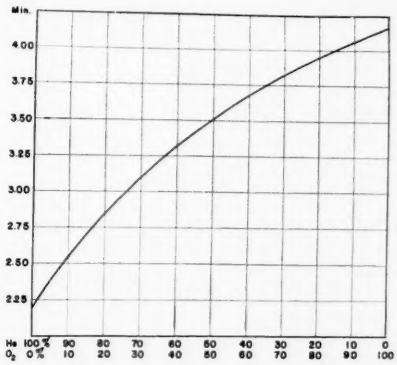

Fig. 4.—Calibration curve obtained with densimometer. The curve shows the time in minutes required for a definite volume of a gaseous mixture, having the composition indicated by the abscissae in the chart, to escape from the closed system through the standard orifice.

rapid flow of gas were discarded. After the air originally in the densimometer has been swept out, the instrument is filled with the gaseous mixture, the composition of which is to be determined. This is accomplished by connecting the densimometer with the ventilation system, closing valve *H*, and manually raising the bell of the densimometer. The gas thus withdrawn from the system into the densimometer is replaced by gas from regulator *E*. The gas in the spirometer bell is washed back into the system, and the bell is then filled again, to secure as representative a sample as possible. The test of the gas is then performed by turning valve *L* to the position shown in Fig. 2 and noting the time required for a portion of the gas in the spirometer *K*, under the pressure caused by the 100 gm. excess weight of the bell, to pass through the orifice at *N*. Two marks 50 mm. apart on the counterpoise cord (Fig. 3) designate the volume to be measured. The time required for these two marks to pass a fixed point is a measure of the rate of effusion of the gaseous mixture. From the results of calibration tests of the densimometer with ordinary air, pure oxygen, pure helium, and various helium-oxygen mixtures, the calibration curve in Fig. 4 has been derived. This curve indicates the percentages of oxygen and helium in the gaseous mixture in the system, according to the established rate of effusion from the densimometer. The practicability of this instrument is demonstrated by the fact that a second densimometer was constructed and adjusted to

*Squibb's heavy California mineral oil.

have the same calibration curve for standard orifices. If dust or other foreign material clogs the orifice, it is best to replace the disk by another tested disk rather than to attempt to clean the orifice. For convenience, several disks are kept at hand in a sealed container. To control the accuracy of functioning of the instrument and to make sure that the orifice is clean, the time for diffusion of room air (3.98 ± 0.04 minutes) is used as a standard.

Automatic Replacement of Oxygen.—To maintain constancy in the composition of the gaseous mixture when the infant is in the chamber, the oxygen consumed by the infant is constantly replaced by an automatic arrangement connected at *Q* (Fig. 2). This consists of a Murrill regulator,[3] which has its bell floated by a cork ring attached at *o, o*. As the volume of the gaseous mixture in the closed system is decreased by the infant's consumption of oxygen (the carbon dioxide produced by the infant is removed by the soda-lime), the tendency for reduced pressure in the system causes replacement of the oxygen from container *E*. As the bell of this instrument falls, it causes valve *G* to be opened, admitting oxygen from the supply line. By a tee dipping into the bottle *F*, containing water, oxygen from a cylinder is constantly supplied under approximately 25 mm. of water pressure to the valve *G*, at a rate of 30 to 50 c.c. per minute. As the bell is raised by the admittance of oxygen, the valve *G* closes and the excess oxygen escapes through bottle *F*. But if valve *G* is open, oxygen will be supplied to the container *E* without contamination, any excess oxygen escaping into the room. As the chamber, with its blower and connecting pipes, has a total capacity of 40 liters, it would contain 10 liters of oxygen when a 25 per cent oxygen mixture is used. If for any reason oxygen failed to be supplied, the chamber would continue to have sufficient oxygen for the infant's needs for at least two hours (the rate of oxygen consumption of these infants has been found to be approximately 20 c.c. per minute) without the oxygen percentage being reduced to an unphysiologic level.

Use of Other Percentage Mixtures of Helium and Oxygen or of Mixtures of Other Gases.—Some infants have benefited by the gas mixtures of low density, but others have required higher oxygen concentration to improve their condition. The oxygen content of the chamber air can be readily increased by admitting oxygen through the valve *V* (Fig. 2) until a calculated quantity of gas in the chamber has been displaced. This is done by stopping the blower, turning valve *V* so that it does not communicate with blower *B* but does communicate with the pipe *A* and the oxygen supply. This insures that the oxygen introduced will go into the chamber. The volume of gas introduced is determined by metering the gas displaced, by connecting to the valve *M* an ordinary wet gas meter or spirometer. If, for example, a mixture of 40 per cent oxygen is desired and the gas already present in the chamber contains 25 per cent oxygen, by displacement of 7 liters of the contents with pure oxygen the oxygen percentage will be increased to approximately 40 per cent. The composition of the new mixture can be readily tested, to insure that the desired percentage of oxygen has been attained. This new percentage will then be automatically maintained, as the oxygen used by the infant will be replaced by the automatic arrangement. In some cases it is desirable to use a mixture of carbon dioxide and oxygen as a respiratory stimulant. This mixture can be admitted in the same manner as described above for enrichment of the oxygen content of the chamber air. When the carbon-dioxide and oxygen mixture is used in the chamber, the ventilation system must not be in operation, as the soda-lime would remove the carbon dioxide. When it is desired to resume the use of the chamber with some other gaseous mixture, the mixture of carbon dioxide and oxygen should be swept out into the room and not through the ventilation system, as otherwise the carbon-dioxide absorption capacity of the soda-lime will be exhausted unnecessarily soon and the technical problem will be encountered of compensating rapidly for the decrease in volume of the gas in the system.

Test for Tightness.—The apparatus is readily tested for tightness by closing valve *Q* to the system, having valves *M* and *L* open to the spirometer, and valves *S* and *V* in the position shown in Fig. 2. The bell of spirometer *K* (which has been overweighted by 100 gm. for use as a densimometer, see page 65) is exactly counter-

balanced by attaching a 100 gm. weight to the counterpoise cord; the level of the bell is then noted, and the weight is removed. This places slight pressure on the system, because of the original overweighting of the bell. After fifteen or twenty minutes the weight is replaced, and if the system is tight, the bell should return to its original level. Slight changes in temperature and slight changes in pressure on the chamber, caused, for example, by placing something on the cover, will alter the apparent volume of the system.

ACTUAL USE OF INCUBATOR

In actual use this incubator has proved excellent in providing the essential conditions for infants needing special care. The temperature is adequately maintained and, even when the chamber is open, the chamber walls prevent marked exposure of the infant to cold. The humidity is maintained in the vicinity of 90 per cent by the use of Wilson soda-lime. Our experience with this incubator has been confined to infants of diabetic mothers. These infants have required attention usually every four hours, to obtain blood samples for sugar determination and for other care. Over a period of four hours, with the chamber sealed, the composition of the gas has been held essentially constant in all cases. The infant is visible through the large window (which could be even larger, if desired) and is readily accessible in the event that immediate attention is needed. It is frequently helpful to have little or no covering on the infant, to facilitate observation and to avoid any possible hindrance to respiration. In this case, the temperature can be held at such a level that the infant will require little or no covering.

Between May, 1936, and May, 1939, ten infants of diabetic mothers were placed in the oxygen-helium incubator in an attempt to combat neonatal asphyxia. The clinical picture associated with fatal asphyxia neonatorum in our experience had been slight respiratory excursion, rising temperature, long periods of apnea and cyanosis, and the development of terminal râles. For many years this picture had been attributed to hypoglycemia due to maternal insulin or hyperplastic islet tissue. The latter is an almost universal finding at autopsy. Our own belief, however, was that hypoglycemia could not be the responsible factor, as it occurs in normal infants without abnormal behavior, is remedied easily by glucose, and the seizures observed in our children were found to occur with blood sugar values above normal and at normal levels as well as below normal. Eventually, through the work on hormones by Smith and Smith[4] and later the prolan determinations by White and Hunt,[5] it became apparent that the fatalities could be predicted by a knowledge of the prolan-estrin balance and prevented by substitutional estrin and progesterone therapy. Thus, among the infants of 14 mothers whose values for prolan were maintained at a normal level by treatment with massive doses of estrin and progesterone three to six weeks prior to delivery, there were 2 deaths, 1 neonatal associated with asphyxia pallida in a premature infant and 1 stillbirth. In the latter instance, the mother's therapy had been omitted. Among the infants of twelve mothers with supernormal values for prolan, there were 6 fatalities, 4 associated with prematurity and asphyxia and 2 stillbirths.

Ten infants were placed in the incubator, all of whom had respiratory difficulties or were cyanotic. The mothers of 6 of these had supernormal values for prolan and their infants were, therefore, in the group in which the mortality rate was high. Despite the oxygen-helium treatment, 3 of these infants died. Hence this treatment does not always result in a successful outcome in this particular complication. Of the 4 infants whose mothers had normal values for prolan, all survived, but we know now that this was to be expected in nearly 100 per cent of these cases. One infant, we believe, was distinctly helped. This infant, who had aspirated amniotic content and for whom the pediatrician had given a fatal prognosis, had long periods of cyanosis without periods of apnea. The cyanosis was relieved when the infant was placed in an atmosphere of almost pure oxygen. She remained in the incubator for forty-eight hours, and then behavior became entirely normal. Two other infants also survived, being apparently aided to some extent by the oxygen-helium treatment. Although this treatment was not successful in all instances in preventing respiratory

failure, in general the infants were less cyanotic and respiration was better when they were in the controlled atmosphere of the incubator.

SUMMARY

An incubator is described in which an infant can be kept at the proper temperature and humidity, with proper ventilation and, to facilitate respiration, in an atmosphere containing a known and controlled mixture of oxygen and helium. A densimometer serves to determine the composition of the gaseous mixture within the chamber and to make certain that this composition remains constant during its use. When necessary, a mixture of carbon dioxide and oxygen can be used as a respiratory stimulant. Originally the incubator was designed for newborn infants of diabetic mothers, in an attempt to combat neonatal asphyxia, and the equipment has proved helpful in several instances. Subsequently it was found that the respiratory failure of such infants can be successfully prevented by prenatal hormone therapy. The clinical experience with the incubator is discussed.

REFERENCES

(1) *Barach, A. L.:* J. Clin. Investigation **15**: 47, 1936; J. A. M. A. **107**: 1273, 1936. (2) *Eversole, U. H.:* J. A. M. A. **110**: 878, 1938. *Sykes, W. S., and Lawrence, R. C.:* Brit. M. J. **2**: 448, 1938. (3) *Murrill, P.:* J. Am. Chem. Soc. **20**: 501, 1898. (4) *Smith, O. W., and Smith, G. V.:* AM. J. OBST. & GYNEC. **33**: 365, 1937. (5) *White, P., Titus, R. S., Joslin, E. P., and Hunt, H. M.:* Am. J. M. Sc. **198**: 482, 1939.

LEUCEMIC INFILTRATION OF THE FEMALE INTERNAL GENITALIA AS A CAUSE OF VAGINAL BLEEDING

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THE leucemias have always constituted a sphere of medicine into which the gynecologist rarely, if ever, entered. The patient suffering with leucemia would come to the surgeon because of enlarged lymph nodes, to the internist because of an enlarged spleen, or to the dermatologist because of infiltrations of the skin. In the case reported in this paper, the leucemic patient came to the gynecologist because of vaginal bleeding, and the constitutional disease was discovered by investigation of the cause of the bleeding. Since women are being educated to the importance of ascertaining the cause of any abnormal vaginal bleeding, some cases of leucemia may be discovered and diagnosed by the gynecologist.

Leucemic infiltration of the female genitalia has always been a rare entity, although it may have been present in some cases where it was either undiscovered or not diagnosed.

The textbooks and handbooks in gynecology (with one exception) make no mention of a relationship between leucemia and pelvic pathology. MacCallum refers to a case of a lymphoid nodule in the cervix uteri extending to the vagina, with ulceration and bleeding. At autopsy there was found "an infiltration of lymphoid cells in many of the organs in association with a leucemic condition of the blood." Leucemic infiltration may occur in any part of the body, although, as noted by

Ewing[1] and Stout,[2] infiltration of the genitalia is the rarer form. Rusch[3] in 1914, reported a case of leucemic infiltration of the labium minus and also referred to a case of Herz (Zit. bei Arzt und Fuhs) in which there was a similar infiltration in the posterior commissure of the vagina. Kulka[4] in 1932, reported a case of lymphatic leucemia in which the infiltration of the clitoris assumed such a form that it was mistaken for a carcinoma.

As for the infiltration of the internal genitalia, Schlagenhaufer[5] seems to have been one of the earlier authors to describe it. In his case the patient had uterine bleeding besides bleeding both subcutaneous and from the gums. This was a case of lymphatic leucemia, and examination of the entire uterus, the ovaries and parametria at necropsy revealed a leucemic infiltration in all of them, besides a chloroma of the fundus of the uterus. Thaler[6] reported an autopsy in a case of acute leucemia in a young woman who had tonsillar abscesses and profuse vaginal bleeding (uncontrollable). Histologic examination showed a leucemic infiltration of the tubes; the uterus and ovaries were uninvolved. The infiltration was described as being composed of lymphoid and myeloid elements (the latter elements may have been due to the fact that there was a purulent salpingitis, bacteriologically identical with the throat culture).

Geipel[7] in 1920, presented the necropsy findings in two cases of lymphatic leucemia. In one case there was a heavy lymphocytic infiltration of the uterus, tubes, and ovaries (the endometrium being the least involved). In the other case, the infiltrate was present only in the deeper layers of the endometrium (the tubes and ovaries were not examined). In both cases there was an atrophy of the endometrium, and the cervix showed a minimal infiltration, and this, for the most part, perivascular.

Brakemann[8] also reported an autopsy of an acute leucemic patient in whom the ovaries, tubes, entire uterus, and vagina were involved with the infiltration. Parenthetically, we might mention that he was the only one to intimate a relationship between the vaginal bleeding and the leucemic infiltration. He stated that irregular profuse vaginal bleeding associated with bleeding from other bodily orifices should suggest leucemic involvement of the genital organs.

Poynder[9] reported a case of chloroma of the uterus discovered at autopsy. This patient had had severe metrorrhagia for several months before death. A diagnosis of acute myelogenous leucemia was made from the findings at autopsy, although there had been no blood count done before death. This case and that of Schlagenhaufer are the only ones in which the infiltration was made evident by this greenish tumor in addition to the usual infiltration.

Neumann[10] referred to a patient with myelogenous leucemia whom he had curetted twice, but in whom he had found no infiltration. He also referred to necropsies in cases of myelogenous leucemia reported by Laubenberg, Geipel, and Bower and Clark, in which there was no infiltration of the genital organs.

In 1934 Pietro[11] reported the autopsy findings in a case of leucemia where he found that the leucemic infiltration had involved, among other organs, the cervix and right ostium of the Fallopian tube. The cervix was so heavily involved that there appeared to be a tumor in it on gross examination.

Held and Kieve[12] reported a case of acute myelogenous leucemia with retrobulbar and cervical tumors. Autopsy revealed a round cell infiltration of numerous organs including the cervix, causing a "tumor" of the latter. Since the white blood cell count was 8,800 with a hemogram showing 19 per cent monocytes, it seems that this case might fall more readily into the category of a lymphosarcoma rather than into that of a myelogenous leucemia.

Villata[13] performed autopsies on two cases of lymphatic leucemia; and on histologic examination of the uterine wall he found lymphocytic infiltration of all three layers.

Novak[14] discussed the occurrence of abnormal vaginal bleeding in cases of leucemia. He quoted Virchow as to the frequent association of menstrual disorders with leucemia. Menorrhagia and metrorrhagia occurred more commonly than deficient menstruation. He also noted that Mosler found in 21 cases of leucemia 16

which showed some form of menstrual anomaly. In many, menstruation was entirely absent and in only 2 of the cases was there any profuse menstruation present.

Kahn[15] reported a case of a patient, aged 45 years, with acute leucemia who had had regular menses until two weeks before admission to the hospital. At that time she began having profuse uterine bleeding which persisted until, and was the cause of, her death in spite of all attempts to stop the bleeding. Nothing abnormal was found on pelvic examination and no autopsy was done.

McDonald and Waugh[16] on July 26, 1939 reported a case of leucemic infiltration of the endometrium, found in a living woman.

The case report which follows is that of a woman who complained of vaginal bleeding, and investigation of the pelvis led to a diagnosis of lymphatic leucemia through biopsies of the endometrium and of the cervix.

A white widow, aged 67, complaining of vaginal bleeding of one year's duration, as well as weakness and fatigability during the same period, presented herself for the first time on Feb. 20, 1939. The family history was irrelevant, except that the patient's husband died of pulmonary tuberculosis twenty-five years ago.

The patient had typhoid fever at twenty-two years of age. Three years ago she had a squamous cell carcinoma of the urethral meatus treated with radium. Two years ago she had a recurrence approximately 1.5 cm. within the urethral canal, which was successfully treated with radium, and she has had no recurrence since then. Questioning as to systemic history revealed that the patient was troubled with frequent colds, cough, and dyspnea upon moderate exertion, as well as arthritis of her hands and knees.

She had two pregnancies. One of these terminated in a normal full-term infant; the other in a spontaneous abortion at four months.

The catamenia began at the age of nineteen or twenty years and occurred regularly every month. Each period lasted three or four days. The menopause occurred twenty-five years ago.

From the time of her menopause, twenty-five years ago, the patient did not have any vaginal discharge or bleeding until the onset of the present illness. During the previous year she had had vaginal discharge of red blood without any clots, necessitating the use of two sanitary napkins during the day and one napkin through the night.

PHYSICAL EXAMINATION

The patient was an obese woman with a pallor of the skin, but not a corresponding pallor of the mucous membranes. The pertinent positive physical findings were: Bilateral submaxillary glands palpable, enlarged, firm, freely movable; blood pressure 180/110; the heart was enlarged slightly to the left by percussion. The spleen was enlarged to 3 cm. below the costal margin; there was a reducible left inguinal hernia. There was a moderate amount of bleeding from within the vagina upon examination. A small cyst was present at the posterior fourchette. The vaginal mucosa was fairly smooth except for the left portion of the anterior fornix and the entire posterior fornix. Numerous discrete, small nodules, each about the size of a pinhead, could be felt in the mucosa in these areas. The cervix was enlarged to about three times the normal size in a patient this age (approximately 5 cm. by 3 cm.) by a soft, irregular tumor (almost the consistency of a cervix in a pregnant patient). Examination of the uterus revealed nothing abnormal, and it was freely movable. No abnormal masses or tenderness were found in the adnexal regions. By speculum examination, the cervix was found enlarged, as described above, with free bleeding coming from it. The color, consistency, and appearance could best be compared to that of the cortex of a kidney. A biopsy was taken of the endometrium with a suction curette and a biopsy was also taken of the cervix.

Laboratory Data.—Urine: Albumin + with many red blood cells and white blood cells on microscopic examination of the sediment. Examination of a voided specimen after cessation of bleeding showed a trace of albumin with many white blood cells present on microscopic examination.

April 8, 1939. Platelet count—202,100/c.mm.

Bleeding time = 1 minute. Clotting time = 3¾ minutes.

Basal metabolic rate + 11 per cent. Kahn—negative.

BLOOD COUNTS:	R.B.C.	W.B.C.	STAB	SEGS	JUV.	EOS.	BAS.	LYMPH.	MONO.
4/ 5/39	5,000,000	33,350	0	20	0	1	1	70	8
4/11/39	4,700,000	35,000	0	20	0	1	0	75	4
4/24/39		27,700	0	22	0	0	1	74	3
4/26/39		26,250	1	22	1	0	0	73	3
4/28/39		17,900							
5/ 1/39		28,800							
5/11/39		12,750	1	42	0	1	0	47	9
5/22/39		14,200	1	44	0	3	0	46	5

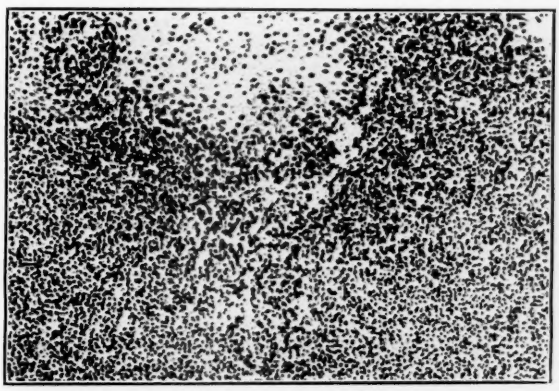

Fig. 1.—Cervix showing infiltrated stroma and overlying epithelium. ×140.

Roentgenograms.—Chest: There was some suggestion of increased width in the right hilar area of the mediastinum. There was cardioptosis of the heart shadow and increased dimensions, particularly toward the left side. *Knees:* There were marked hypertrophic osteoarthritic changes; and, in addition, the joint cartilage of the right knee showed almost complete absorption and partial ankylosis. *Hands:* The phalangeal joints of both hands showed marked hypertrophic bone lipping and the distal joint cartilage showed marked absorption changes. *Abdomen:* There was a splenic enlargement, and the spine and pelvic margins showed hypertrophic bone changes.

On April 19, 1939, a dilatation and curettage of the uterus was done. The cavity and cervical canal measured 2½ inches. Curettage of the uterine cavity showed it to be regular, and a very scant amount of curettings were obtained. There were no polyps or irregularities felt with the curette. The small cyst at the fourchette was excised for biopsy.

On April 22, 1939, deep roentgen ray therapy was begun over the area of the spleen with a 200 K.V. machine. Five treatments of 100 r. each (measured at the skin) were given approximately every other day. The portal used was 10 cm. by 10 cm. with a filter consisting of ¾ mm. Cu at a target skin distance of 50 cm. A constant check was made of the blood count during this therapy. After several treatments had been administered all the vaginal bleeding ceased.

On May 11, 1939, examination showed the spleen to be much smaller, the tip being just palpable at the costal margin. The cervix had decreased in size, being approximately 3 cm. by 2 cm., and the nodulations in the vaginal mucosa in the fornices had entirely disappeared.

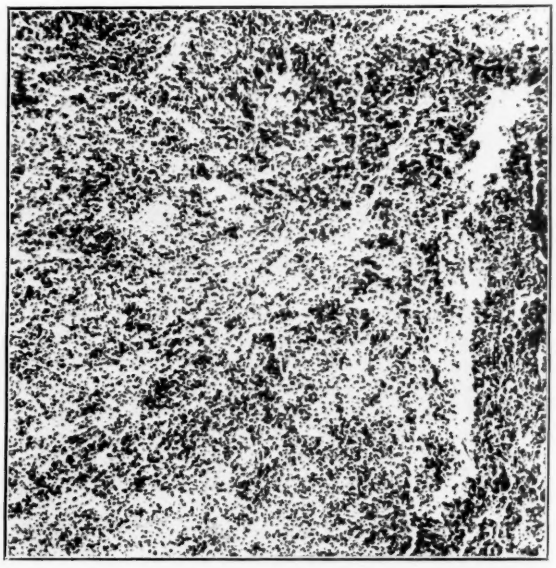

Fig. 2.—Shred of tissue obtained upon curetting uterine cavity. ×140.

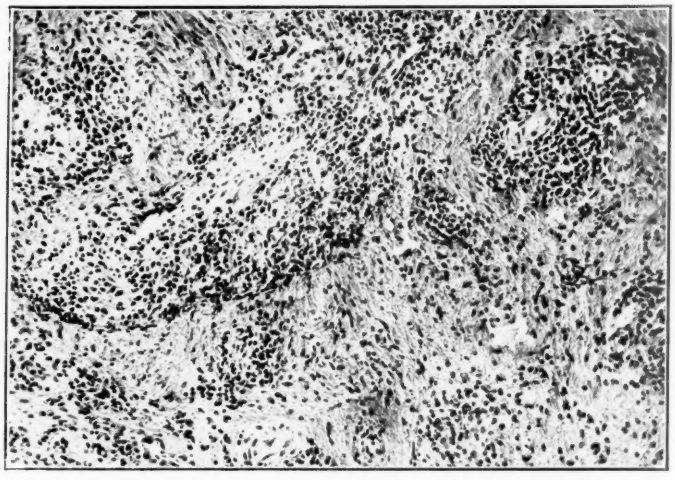

Fig. 3.—Cervix showing stroma and small areas of infiltration remaining after therapy. ×140.

HISTOPATHOLOGY

Examination of the tissue from the cervix (Fig. 1) showed a heavy round cell infiltration of the entire fibromuscular stroma of the cervix. This infiltration did not involve the cervical glands or the overlying epithelium. It was found to be the lymphocytic cell (large and small) infiltration which composes leucemic infiltrates.

In some sections there were areas of stroma free of the infiltration. This infiltration should not be interpreted as an infiltration of acute or chronic inflammation or of granuloma.

In the small shred of tissue obtained upon curetting the uterine cavity, the same infiltration of the stroma (Fig. 2) was found as was present in the cervix. The absence of endometrial glands in this shred of tissue was not unexpected, since this was a senile endometrium.

In Fig. 3 is represented the cervical fibromuscular stroma after the completion of, and response to, therapy. The stroma could be readily seen with the round cell infiltration occurring in areas here and there.

The cyst removed from the fourchette proved to be a sebaceous cyst.

DISCUSSION

As may be noted in the discussion of the literature in the earlier part of this paper, all the cases of leucemic infiltration of the internal genitalia were those found at autopsy. Never before had a case of this sort been reported in a living woman until the one reported in July, 1939, by McDonald and Waugh.[16]

Not any less interesting than the diagnosis of leucemic infiltration of the genitalia in a living woman is the fact that the examination of the tissue removed by biopsy led to the diagnosis of her constitutional disease of leucemia. When the tissue, removed by biopsy, was examined under the microscope, the impression was that the lymphocytic infiltrate was probably due to a leucemia. Blood counts, hemograms, and the splenomegaly corroborated this impression. (The hemograms were studied in the fixed stained smear as well as with the supravital stains.)

Since the involvement is present in the vagina, cervix, and endometrium, it would be logical to assume that the myometrium is also involved.

Kahn[15] reviewed 8 cases of leucemia in female patients in the hospital records. In 6 of them the menstruation was undisturbed, but in the other 2 the menstrual bleeding was excessive, prolonged, and occurred with increased frequency. The question arises whether in these two cases of leucemia there might not have been an infiltration of the internal genitalia as a cause for the abnormal vaginal bleeding.

In this case the involvement could be studied as well as the beneficial effect of the therapy. The excellent response to the irradiation over the spleen is manifested by the diminution in the blood count and improvement in the hemogram, as well as by the disappearance of the bleeding and of the nodular infiltration of the vagina and by the reduction in the size of the cervix.

Brakemann[8] was the only author who intimated a possible relationship between the leucemic infiltration of the genitalia and the vaginal bleeding, while McDonald and Waugh[16] state that there is a definite relationship. We believe there is a direct relationship as proved by the disappearance of the bleeding after the therapy was instituted. There is nothing else to account for the vaginal bleeding as far as any disturbance in the clotting mechanism of the blood, adnexal tumors, polyps, or vaginitis is concerned. The platelet count and bleeding and

clotting time were all found to be normal. The cessation of bleeding after irradiation over the spleen would contradict any claim for any of these as the etiologic agent as well as any consideration of a hormonal basis.

One other case has come under our observation in which a cervical polyp was removed, and upon routine histopathologic examination a lymphoid cell infiltration was found in it, as well as in several areas of the fibromuscular stroma of the cervix. At the time, the blood picture was quite suspicious, but at a later date a study of the bone marrow could not corroborate it as a proved case.

Since the age incidence of leucemia corresponds fairly well to that of the menopause, it does not seem too far fetched that other cases of leucemia may be discovered when patients come to the gynecologist because of abnormal vaginal bleeding (either just before or after the menopause). Any competent gynecologist confronted with a problem like this would remove tissue for histologic study (cervical, if the cervix were involved, and endometrial). Then examination of the tissue may lead to the possible diagnosis of a leucemia instead of an "empirical" diagnosis of menopausal bleeding or of endocrine disturbance. One of the most likely mistakes is that the tissue removed for microscopic examination may be diagnosed as chronic endocervicitis or chronic endometritis on cursory examination. The cases of early involvement may show a minimal amount of infiltration; or else a section may be obtained which would show infiltration in one portion and not in another. However, this is not so likely to disconcert the pathologist when the entire section is carefully examined.

All the cases of this infiltration of the genitalia are reported from foreign countries and none (except for the case of McDonald and Waugh) have ever been reported from this country. Yet there is no geographic distribution of the disease. A logical deduction would be that there are probably quite a few cases in which the genital infiltration is never discovered. It seems to be a possibility that there may be an infiltration localized to the uterine wall, as described in Villata's[13] cases, and thus the cervix would fail to show any abnormality. The cause for the bleeding in a case like this would be obscure and careful examination of the tissue removed by curettage could lead to the diagnosis. (These latter lines of assumption were written before the publication of the case of McDonald and Waugh and are proved by that case.)

SUMMARY

This is a case of chronic lymphatic leucemia. The leucemic infiltration of the endometrium, cervix, and fornices of the vagina is discovered for the first time in a living woman. Furthermore, the examination of the tissue removed by biopsy led to the diagnosis of the disease. The relationship between the infiltration and abnormal vaginal bleeding is discussed. The beneficial response to therapy is demonstrated.

The authors wish to express their appreciation for the cooperation of Drs. Carl V. Moore and Harry Agress in the hematologic studies.

REFERENCES

(1) *Ewing, J.:* Neoplastic Diseases, Philadelphia, 1934, W. B. Saunders Co., p. 345. (2) *Stout, A. P.:* Human Cancer, Philadelphia, 1932, Lea and Febiger, p. 811. (3) *Rusch:* Arch. f. Dermat. **119:** 524, 1914. (4) *Kulka, H.:* Arch. f. Gynäk. **149:** 450, 1932. (5) *Schlagenhaufer:* Arch. f. Gynäk. **95:** 1, 1912. (6) *Thaler, H.:* Zentralbl. f. Gynäk. **44:** 436, 1920. (7) *Geipel:* Zentralbl. f. Gynäk. **44:** 176, 1920. (8) *Brakemann, O.:* Ztschr. f. Geburtsh. u. Gynäk. **86:** 23, 1923. (9) *Poynder, L. M.:* Étude d'un cas de Chlorome de l'Utérus, Thèse d'Universite de Lausanne, 1930. (10) *Neumann, H.:* Zentralbl. f. Gynäk. **55:** 156, 1931. (11) *Pietro, C.:* Arch. ital. di anat. e histol. pat. **5:** 397, 1934. (12) *Held, E., and Kieve, P.:* Helvet. med. acta **4:** 371, 1937. (13) *Villata, I.:* Riv. ital. di ginec. **21:** 287, 1928 (from International Abstract of Surgery in Surg. Gynec. Obst.). (14) *Novak, E.:* Menstruation and Its Disorders; Obstetrical and Gynecological Monograph, 1921. (15) *Kahn, M.:* J. A. M. A. **99:** 1563, 1932. (16) *McDonald, R. J., and Waugh, J. M.:* Proc. Staff Meet. Mayo Clinic **14:** 465, 1939.

VAGINAL ACIDITY (IN VIVO GLASS ELECTRODE MEASUREMENTS) IN LATE PREGNANCY AND ITS RELATION TO THE VAGINAL FLORA

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A PREVIOUS communication from this department[1] detailed a method for determining the pH of the undiluted vaginal discharge by a quinhydrone microelectrode. It was shown that the acidity varied with the character of the vaginal flora and was higher as the number of the vaginal bacilli of Döderlein increased. In general, the pH was slightly higher in pregnant than in nonpregnant women, and somewhat lower in the upper than in the lower vagina. The available literature up to 1936 was also reviewed.

The recent development of glass electrodes of a high degree of accuracy and in a multitude of designs has stimulated a repetition of this work in connection with certain investigations upon the flora of the vaginas of normal pregnant women in the last weeks of gestation. The glass electrode technique possesses the great advantage of permitting rapid and accurate determinations in vivo at any designated level in the vagina.

MATERIAL

Two hundred ante-partum women admitted to the University Hospital for delivery and post-partum care were subjected to glass electrode pH determinations on the vaginal discharge. In addition, studies were made of (a) gram-stained spreads of the discharge, and (b) cultures for the Döderlein bacilli, for monilia, and for the *Trichomonas vaginalis,* according to the following techniques.

TECHNIQUES

Glass Electrode Hydrogen-Ion Determinations.—The Cameron pH-meter (Fig. 1) consists of a "detector unit" (containing an amplifying tube and carrying a saturated calomel electrode and a glass electrode), a potentiometer calibrated directly in terms of pH, and a ten-foot connecting cable to permit convenient operation. With the patient in the lithotomy position, the detector unit is held close to the vulva, the glass electrode is inserted into the vagina to the desired depth, and the

circuit is completed by placing in the vagina beside the electrode a sturdy blunt-tipped capillary tube which is connected with the potassium-chloride reservoir of the calomel electrode by a rubber tube filled with saturated potassium chloride. The difference in potential between the two electrodes depends upon the pH of the vaginal discharge and is indicated as such on the potentiometer. The procedure, which can be completed in a few seconds, rarely causes any discomfort, and permits rapid readings at several levels.

The glass electrodes are readily cleansed between tests with soap and water and alcohol. When not in use they should be kept in water. The potassium-chloride junctions are not so easily cleansed and it is advisable to have several available in order to conserve time. After use they are immersed for ten minutes in 2 per cent phenol solution, washed with soap and water, and rinsed with distilled water under pressure. Before they are used again they are filled with saturated KCl solution from the reservoir, care being taken to exclude all bubbles.

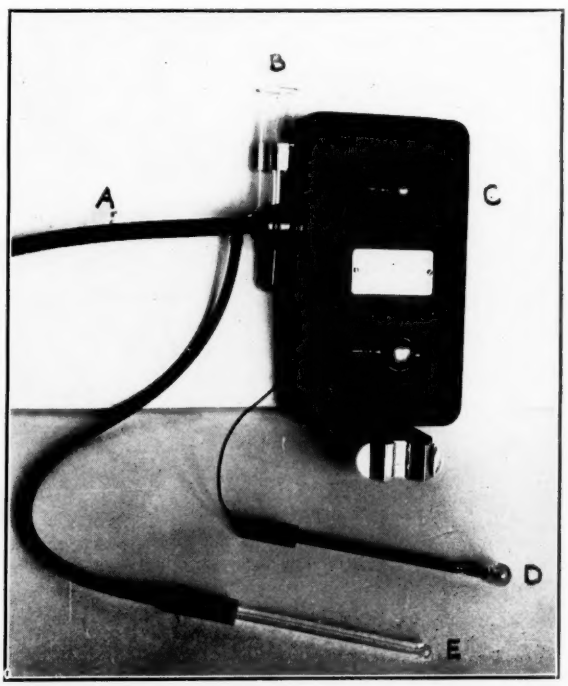

Fig. 1.—The Cameron pH meter. *A*, Cable to potentiometer; *B*, calomel electrode; *C*, detector unit; *D*, glass electrode; *E*, potassium chloride junction.

The difference in temperature between the glass electrode (vaginal temperature) and the calomel electrode (room temperature) disturbs the potentiometer readings so slightly (one-half times 0.015 pH per 5° C. temperature difference times the pH unit difference between the point of calibration, pH 4.0, and the test level, 3.96 to 6.99) that the corrections have not been introduced.

Early in the study certain difficulties were experienced in obtaining constant readings because of one or more of the following factors: (1) Faulty glass electrodes due to "bubble etching," an error which can be eliminated by standardizing the electrodes with a known buffer of pH 4.0 and checking them against a buffer solution of pH 7.38. (2) Contact of the glass electrode with the cervix which exposes it to both an alkaline (the cervix) and an acid (the vaginal wall) environment, thus making constant readings impossible. Pulling the electrode away from the cervix obviates this difficulty. (3) Failure to complete the circuit, so that no read-

ing can be obtained. Rotation of the glass electrode and of the KCl junction tube, and occasionally flushing a small amount of the KCl solution through the tube will usually restore normal operating conditions promptly.

BACTERIOLOGIC STUDIES

Consistent attempts were made to take the material for spreads and cultures from the portion of the vaginal wall contacted by the tip of the glass electrode. For the lower vagina, the labia were separated widely and the discharge collected from the area immediately inside the closed portion; while a sterile Graves' speculum was employed to expose the higher portions of the canal. Three swabs were inoculated from each patient and were treated as follows:

Swab 1 was spread directly on a clean glass slide, and then dropped into a tube of 5 per cent human serum in Ringer's solution over a placenta infusion agar slant. The original spread was stained by the Hucker modification of the Gram technique and examined under the oil-immersion lens. The flora was classified according to Schroder.[1] The culture was incubated at 37° C. for eighteen to twenty-four hours, when the sediment was examined for motile trichomonads.

Swab 2 was placed in a tube of 1 per cent lactose broth and incubated in a McIntosh-Fildes anaerobic jar for forty-eight hours. One drop of this culture was then stained and examined for gram-positive rods, while a second drop was inoculated onto the surface of a Difco tomato agar plate, which was incubated in an

Fig. 2.

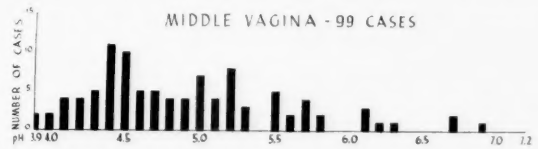

Fig. 3.

Figs. 2 and 3.—Glass electrode measurements of acidity in the middle and lower vagina.

atmosphere containing 10 per cent carbon dioxide for forty-eight hours, and then examined under the low-power lens. If the colony development was not typical, the growth was transferred to a slide and stained with the Gram technique. The presence of discrete colonies with yellowish centers or translucent colonies with filamentous offshoots and the demonstration of typical gram-positive rods were assumed to indicate the presence of the vaginal bacilli of Döderlein.

Swab 3 was rubbed over the surface of a Sabouraud's agar slant and then used to inoculate a tube of Sabouraud's broth. After forty-eight hours, visible growths were transferred to a slide and stained by the Gram technique. The presence of large gram-positive ovoid cells and budding conidia was assumed to show the presence of "monilia." The fungus was then isolated in pure culture and stored for future study of mycelium and ascospore production (the "monilia" produce the former but not the latter).

RESULTS

Vaginal pH.—The pH readings agreed closely with those previously reported[1] for pregnant women, and confirmed the earlier observation that the discharge in the lower vagina is usually less acid than that obtained from the middle portion of the canal, especially when the discharge is scanty and does not flow readily. The distribution of the pH values in the middle vagina is indicated in Fig. 2 and that in the lower vagina in Fig. 3.

TABLE I. INDIVIDUAL DIFFERENCES IN pH OF THE MIDDLE AND LOWER VAGINA

PATIENT	LOWER VAGINA pH	MIDDLE VAGINA pH	DIFFERENCE IN pH
61	6.30	5.29	1.01
62	7.20	6.88	0.32
163	5.96	5.84	0.12
165	4.20	4.09	0.11

Table I shows typical differences obtained in individual patients.

Relation Between pH and Vaginal Flora.—The relation between the vaginal acidity and the flora as observed in the stained discharge is shown in Table II.

TABLE II. RELATION BETWEEN pH AND VAGINAL FLORA

(Based Upon 140 Satisfactory pH Measurements)

TYPE OF FLORA (SCHRODER)	HYDROGEN-ION CONCENTRATION					
	MIDDLE VAGINA			LOWER VAGINA		
	CASES	AVERAGE	RANGE	CASES	AVERAGE	RANGE
I	46	4.58	3.96-5.72	14	5.13	4.43-6.30
II	31	5.03	3.99-6.10	25	5.13	4.16-5.98
III	17	5.69	4.92-6.88	7	5.54	4.58-7.20

The bacterial flora observed in spreads from the lower vagina (just inside the introitus) frequently does not agree with the Schroder type expected on the basis of the measured pH. Individual cases brought out this fact more strikingly than do the average values presented in the table, and suggest that some factors other than pH have a role in the control of the bacterial growth near the introitus.

Döderlein Bacilli Cultures.—Among the 195 cultures for Döderlein bacilli (5 patients were not cultured for this organism) in lactose broth, 185 contained gram-positive rods morphologically similar to the vaginal bacilli. On the tomato-agar subculture plates, there were 173 positive cultures and four plates were overgrown by bacterial "spreaders" or molds. Eight of the subcultures did not substantiate the findings in the original cultures, and it is uncertain whether the bacilli observed in the spreads were of the Döderlein group or whether the failure to recover them was due to insufficient anaerobic cultivation.

Among the 200 spreads examined during classification of the discharges, 29 showed no gram-positive rods (Type III). However, gram-positive bacilli were grown in 24 of the 29 original broth cultures from patients with Type III discharges, and in 18 instances the bacilli were identified as Döderlein bacilli in the tomato-agar subcultures. Obviously the absence of gram-positive rods in spreads does not justify the conclusion that there are no Döderlein bacilli in the discharge, but for practical clinical purposes the stained spread offers a convenient index to the character of the vaginal flora.

Monilia Cultures.—Yeast-like fungi were obtained from 68 patients (34 per cent), a figure considerably higher than that (22.4 per cent) recorded in a previous study of cultures from the cervix and posterior fornix,[2] and more than three times that noted in the recent communication of Waters and Cartwright.[3] The majority of the cultures in the present series were obtained from the midportion of the vagina where the pH is somewhat lower than in the cervical region. The use of both Sabouraud's broth and Sabouraud's agar slants slightly increased the number of positive cultures: In 8 instances the slants were positive and the broth negative, whereas in 9 cases the reverse was true.

Satisfactory pH readings were obtained from 30 of the 68 patients who harbored monilia. The range of acidity was from pH 3.96 to pH 6.99, with an average of pH 4.96. Twenty-four of these 30 patients presented Type I or II discharges.

Among the 6 with Type III flora, the pH readings were 4.92, 5.27, 5.28, 5.71, 6.11, and 6.99, respectively, and the growth was relatively sparse on both culture media. The heaviest growth of fungi occurred with the more acid discharges. In 6 of the 9 cases where the organism grew only in the broth medium, the pH range was 3.99 to 6.99, and the average was 5.37.

Trichomonas Vaginalis.—Twenty-three (12.1 per cent) of the 190 trichomonas cultures were positive. This is in sharp contrast to the findings in material taken from the upper vagina and cervix,[2] when 24.0 per cent positive cultures were obtained. It is well known that the trichomonads demand a medium which is not too strongly acid. In 18 of the 23 patients with positive cultures, the pH ranged from 4.55 to 6.38 and the average was 5.58, well above that for the entire series. Twelve of this group of 18 had discharges classified as Type III, 5 as Type II, and only two as Type I. In 8 of the patients with positive trichomonas cultures, monilia were also grown. The pH values in 4 of this group ranged from 4.92 to 6.21, and averaged 5.46.

SUMMARY

The glass electrode technique offers a rapid and convenient method for determining the pH at any desired level in the vagina. In late pregnancy the acidity is highest in the middle portion of the vagina, with the region just inside the introitus being somewhat less acid (see Table I), and the cervix and upper vaginal fornices having an alkaline or only slightly acid reaction. The latter situation is undoubtedly due to the admixture of cervical mucus.

The acidity variations observed in the middle vagina correlate roughly with the type of vaginal flora, and apparently with the content of the vaginal bacilli of Döderlein. The monilia are most frequently present in the more acid discharges, while the trichomonads are favored by a less acid reaction. Consistent with this observation, it is generally true that the fungi are most easily cultivated from the middle vagina and the trichomonads from the upper portions near the cervix. Reported variations in the vaginal pH and in the asymptomatic presence of the trichomonads and the monilia under similar conditions and in comparable groups of patients may be explainable on this basis.

CONCLUSIONS

Varying conditions obtaining at different levels in the vagina under the influence of physiologic factors must be considered in any discussion of vaginal acidity or of the type of flora observed. All of the variations in the vaginal flora cannot be explained by alterations of the vaginal acidity.

REFERENCES

(1) *Oberst, F. W., and Plass, E. D.:* Am. J. Obst. & Gynec. **32:** 22, 1936. (2) *Tucker, W. W., Trussell, R. E., and Plass, E. D.:* Am. J. Obst. & Gynec. **38:** 1055, 1939. (3) *Waters, E. G., and Cartwright, Eakle, W.:* J. A. M. A. **113:** 30, 1939.

PALLIATIVE TREATMENT OF DYSMENORRHEA

With Acetylsalicylic Acid, Phenacetin and Propadrine Hydrochloride

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THE treatment of dysmenorrhea of any type has been difficult especially in young women just beyond adolescence whose mothers will not permit a complete examination. If an examination is permitted, it frequently requires an anesthetic and even then the mother ordinarily will not permit of any radical procedure which might possibly give relief. Moreover many of the procedures are unsatisfactory.

The many medicaments are offered based on two principles: sedation and analgesia, or relaxation of the smooth musculature. Sedatives and analgesics may relieve those mild cases without cramps, but leave the usual "hang-over" of mental depression. They are of little value in the severe cases, while nearly all of the antispasmodics upset the stomach markedly, cause excessive dryness of the mucous membranes, or else are not antispastic enough to be of value, besides necessitating the use oftentimes of hypodermic administration.

For this study, dysmenorrhea was divided into the usual broad classification of primary or functional, and secondary or organic. The functional or primary dysmenorrhea was further divided into: obstructive, hypoplastic, and constitutional. And while it is sometimes impossible to differentiate these clearly and there is marked overlapping, for the purpose of this study the cases have been placed definitely in one or the other of the classes.

It would seem then that anything which would produce relief from pain without any aftereffects should be more than welcome. If, in addition to this, the mental depression could be lifted, much would have been accomplished.

In this study a combination of 5 gr. of acetylsalicylic acid, 3 gr. of phenacetin, and ¾ gr. of propadrine hydrochloride was used. The value of acetylsalicylic acid as an analgesic is well known. It probably has the least depressant action of any known analgesic with most individuals. It is, however, ineffective in severe pain, and especially cramplike pain. It is fortunately tolerated well by most persons and is practically nontoxic. Phenacetin while probably possessing more analgesic properties than "aspirin" is apparently much more depressing in its action, and seems to be especially so during the menstrual period. It also, like "aspirin," is not capable of relieving cramplike pains.

It was felt that the dosage noted of acetylsalicylic acid and phenacetin was small enough to cause but little depression and that the

propadrine hydrochloride was synergistic in that it increased the effectiveness of the other two ingredients, but counteracted any tendency to depression afterwards. In addition to this, it was felt, but not proved entirely, that the propadrine hydrochloride was a marked antispasmodic and decongestant without side effects, and with no possible chance for anuria or nausea. Black[3] and Boyer[4] both found propadrine hydrochloride far superior to ephedrine as an antispasmodic and much less toxic.

The cases were not selected for age or severity, nor for the duration of the condition, but rather as the usual run of patients seen in the office of the general practitioner. They were divided according to the classification given above. In most of the cases the results were reported not only by the patient, but by the mother or relative also, with especial regard to the reaction of the individual to others about her, the temper, depression, and irritability.

The patients were given three capsules daily (except in the terribly severe cases, when the patient received one every three hours) at the very first onset of distress, and continued until the third day of the period. Pain after the third day is not relieved well by this preparation and should lead one to suspect some organic lesion. The capsules were given the first month, then skipped the second month, then repeated the third month in an attempt to cover the variation that may be expected in some women.

DISCUSSION

After a study of 34 cases of primary dysmenorrhea and 4 cases of organic or secondary dysmenorrhea, patients ranging in ages from 14 to 44 years of age, it was very apparent that the combination of acetylsalicylic acid, phenacetin, and propadrine hydrochloride is more effective in the primary type of dysmenorrhea and, it seems, is more effective if taken immediately upon the appearance of symptoms. There is no explanation for the fact that the results are not as good during the last few days of the menstrual period, although generally this makes no difference, for most of the patients are free from pain at that time.

There is a marked effect within a few minutes after taking the capsule, and a few patients showed almost an exhilaration, although it was never enough to keep the patient awake. It has a definite beneficial effect upon the turgescence of the nasal mucous membrane and the light-headedness which is so often seen in women at the time of menses.

The same combination was used by substituting ephedrine for the propadrine hydrochloride; however the effect seemed delayed, and several patients could not tolerate it because of nausea. It also produced a marked tremor in many patients and this seemed to leave a slight after-depression. No nausea or tremor was observed in any of the patients when propadrine hydrochloride was used. A few have reported that the skin felt "goose pimply" for a short period, but that it gave them a sense of exhilaration.

TABLE I. PRIMARY DYSMENORRHEA

NO.	AGE	COMPLAINT	FIRST MONTH	SECOND MONTH	THIRD MONTH	COMMENT
			Neuralgic or Nervous Type			
1	34	Ache and depressed	Relief for 2 days	Usual pain	Relief for 2 days	No effect on time or clotting
2	22	Mild cramps and depression	Complete relief	Usual pain	Complete relief	No effect on time or clotting
3	26	Severe cramps	Partial relief, no loss of time	Usual pain	Partial relief, no loss of time	No effect on time or clotting
4	19	Delayed, cramps	Relief of pain	Usual pain	Relief of pain	Still delayed
5	26	Severe cramps, depression	Complete relief	Usual pain, depression	Complete relief	No delay or change
6	16	Severe cramps	Partial relief, in bed one day	Usual pain, in bed 3 days	Relief, not in bed	No effect on flow
7	22	Pressure and depression	Complete relief	Usual pressure	Complete relief	Period lessened 1 day
8	14	Cramps and irritability	Relief from cramps	Usual symptoms	Relief from cramps	Excessive flow and still irritable
9	16	Cramps	Relief from cramps	Usual cramps	Complete relief	No change at all
			Obstructive or Mechanical			
10	34	Cramps and depression	Complete relief	Usual symptoms	Complete relief	No effect on time or clotting
11	21	Severe cramps, loss of 2 days	Relief, no loss of time	3 days' loss with cramps	Relief, no loss of time	One day less
12	16	Severe cramps, excessive flow	Complete relief	Usual symptoms	Relief from cramps	No change in flow, still excessive
13	26	Backache and pressure	Relief from pain and pressure	Usual symptoms	Relief from pain and pressure	Still has excessive flow, retroversion
14	24	Backache and pressure	Relief from pain and pressure	Usual symptoms	Relief from pain and pressure	No effect on time, anemic. Retroversion
15	14	Cramps and excessive flow	Relief from cramps	Usual symptoms	Relief from cramps	Still has excessive flow, retroversion and stenosis
16	37	Severe cramps	Partial relief	Severe cramps	Partial relief	Cervical repair which left stenosis
17	41	Cramps and depression	Relief	Usual symptoms	Relief	Beginning menopause
18	39	Leg ache and back ache	Relief first day	Usual symptoms	Relief first day	Three pelvic operations
19	40	Leg ache and hysteria	Partial relief	Usual symptoms	Relief, no hysteria	Cervical repair which left stenosis

TABLE I—CONT'D

NO.	AGE	COMPLAINT	FIRST MONTH	SECOND MONTH	THIRD MONTH	COMMENT
			Hypoplasia of Generative Organs			
20	32	Pain after period starts, irregular	Partial relief	Usual symptoms	Partial relief	Infertile, infantile uterus
21	39	Severe backache	Some relief	Usual symptoms	Partial relief	Acute antiflexion, long cervical neck, obese
22	14	Cramps and irregularity	No relief	Usual symptoms	Partial relief	Obese, lethargic and unsanitary
23	15	Cramps, epilepsy depression	Relief from cramps	Cramps, 1 seizure	Relief from cramps	No seizure during months while taking preparation
24	26	General pain and severe depression	Relief from pain and depression	Depression, usual pain	Relief from both	Loses 2 days. None lost while taking preparation
25	27	Amenorrhea, but pain and depression	Relief from pain and depression	Usual symptoms	Relief from pain	Has patent cervix. Periods 6 mo. Pain each month
26	37	Backache and hysteria	Partial relief	Usual symptoms	Partial relief	Long, antiflexed uterus. Fear of pregnancy
			Dysmenorrhea Due to Constitutional Disease			
27	19	Pelvic and backache	Partial relief	Usual symptoms	Partial relief	Incipient tuberculosis. In bed
28	39	Severe abdominal pain and leg ache	Slight relief	Usual pain	Slight relief	Active tuberculosis. Laparotomy 5 yr. ago
29	26	Malaise and depression	Complete relief	Usual depression	Complete relief	Anemic, chlorotic, hypothyroidism
30	39	General body aching	Fair relief	Usual aching	More relief	Marked hypoparathyroidism. Loss of calcium in bones
31	29	Severe cramps, excessive flow	Marked relief	Usual cramps	Marked relief	Severe arthritis, but improving
32	44	Severe cramps	Relief	Usual cramps	Relief	Change of life. Arthritis in all joints
			Migraine Type			
33	23	Severe cramps, migraine	Relief, no attack	Cramps, pain headache and nausea	Relief, no attack	Always had migraine type of pain and headache and nausea
34	42	Aching and migraine attack	Relief, no attack	Usual symptoms	Relief, no attack	Migraine type of headache with nausea

TABLE II. ORGANIC OR SECONDARY DYSMENORRHEA

NO.	AGE	COMPLAINT	FIRST MONTH	SECOND MONTH	THIRD MONTH	COMMENT
1	33	Backache and leg ache	Partial relief	Usual symptoms	Partial relief	Large body uterus, with lacerated cervix
2	43	Severe backache	Partial relief	Usual symptoms	Partial relief	Endometritis and cervicitis
3	29	Backache	Partial relief	Usual symptoms	Relief	3 pelvic operations
4	29	Pelvic pain and backache	Partial relief	Usual pain	Partial relief	Subinvolution, cervicitis. Endometritis

A study was undertaken to determine what effect this preparation might have upon blood pressure. The patient was required to lie down for fifteen minutes during which time the blood pressure was carefully checked. One capsule of the preparation was then given orally, and the blood pressure checked every fifteen minutes for one hour and a half with the patient still lying absolutely quiet. No water or anything else was given and no one allowed in the room.

The patients were divided into three age groups: from 15 to 25 years; from 25 to 35, and from 35 to 45. It was found that variation in blood pressure was very slight, the greatest being 10 mm. of mercury in the systolic pressure at the end of forty-five minutes. This was the case of a young woman who was very excitable, who had a plus metabolic rate of 22 points. The average rise in pressure was four points, generally reaching this peak at the end of sixty minutes. All had dropped to normal at the end of ninety minutes. None displayed a compensatory fall below normal. The diastolic pressure varied not more than two points.

CONCLUSIONS

There are not enough cases in this study, nor could some of the features be well enough controlled to warrant drawing positive conclusions. However, this much is evident; this preparation offers marked relief for the majority of women who suffer distress and depression during the menstrual period. The relief from depression both physically and mentally is often more gratifying to the patient than the relief from pain. (1) It is safe and nontoxic. (2) Its effect is almost immediate. (3) It produces no nausea or dizziness, and no after effect. (4) It does not depress the kidneys, nor does it influence the regularity or the amount of the menstrual flow. (5) It appears to be most effective during the first two days of the period.

The preparation used for this study was made, upon request, by Sharp & Dohme of Philadelphia, Pa.

REFERENCES

(1) *Meyer, H.:* Die Frau als Mutter, 1899. (2) *Davis, A. A.:* Dysmenorrhea: Its Etiology, Pathology and Treatment, London, 1938, Oxford University Press. (3) *Black, J. H.:* Lancet **57:** 101, 1937. (4) *Boyer, W. E.:* Allergy **9:** 509, 1938.

BLOOD STUDIES DURING PREGNANCY AND PUERPERIUM*

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THE occurrence of a physiologic anemia developing during the course of pregnancy has been recognized. A 10 to 20 per cent lowering of hemoglobin may be the result of a hydremia associated with the increased vascular area which exists in pregnancy.

The etiology of the true anemias of pregnancy has not been proved conclusively. A number of factors play a role in the development of these anemias.

Strauss[11] believes that the vast majority of the anemias of pregnancy are of the hypochromic variety which are due either to a direct dietary deficiency or to a deficiency conditioned by gastric anacidity, hypoacidity or associated defects in the presence of fetal demands for blood building materials. Peters and Van Slyke[9] conclude that there is an apparent diminution of the body's supply of hemoglobin. Bethell[2] believes that the anemias of pregnancy are due either to pre-existing iron depletion or to an inadequate intake of protein of high biologic value.

During a recent study of the anemias of pregnancy (Labate[7]), a group of 19 patients were subjected to more intensive study in order to determine some of the etiologic factors which were responsible for the development of the anemic state during pregnancy.

Method.—Nineteen pregnant women who entered the obstetric ward at Bellevue Hospital during the last month of pregnancy either for premature rupture of the membranes, false labor, or for observation remained in the hospital until after delivery. A red blood count, hemoglobin (Sahli), reticulocyte count, hematocrit, and plasma protein determination were performed on admission. These were repeated on alternate days during the remainder of the prenatal period and during the first ten days following delivery. A gastric analysis was done during the ante-partum period and again on the eighth day post partum. The results of the study of the gastric analyses have been reported in a previous communication (Labate[8]).

The hematocrit readings were obtained using the method described by Wintrobe.[13] Six milligrams of ammonium oxalate and 4 mg. of potassium oxalate per 5 c.c. of venous blood were used as anticoagulant. In this solution the volume of the erythrocytes remains unaltered (Heller and Paul[6]).

The plasma protein determinations were done by the falling drop method (Barbour and Hamilton[1]).

Results.—Eight patients who had a blood loss of 350 c.c. or more, at the time of delivery, were excluded from the present analysis. The average red blood count of the 11 remaining women rose from 3.47 million during the thirty-eighth week of pregnancy to 3.70 million in the fortieth week. The average hemoglobin also rose from 9.6 gm. to 10.16 gm. and the average cell volume from 34.7 to 37.7 per cent

*This work was carried out by means of a grant from The Bovinine Company, Chicago, Illinois.

during the same interval (Tables I and II, Fig. 1). The plasma proteins increased from 7.28 mg. per cent to 7.71 mg. per cent between the thirty-eighth and fortieth weeks.

On the day of delivery, there occurred a slight drop in the red blood count and hemoglobin, but a temporary secondary rise was noted on the second day post partum. This increase in red blood count and hemoglobin was lost on the fourth day, but thereafter a slow rise ensued. The red blood count resumed a practically normal level on the tenth day. The hemoglobin, however, remained 9 per cent below normal (Table I, Fig. 1). Dieckmann and Wegner[5] also noted that the hemoglobin, two weeks post partum, was 17 per cent below normal.

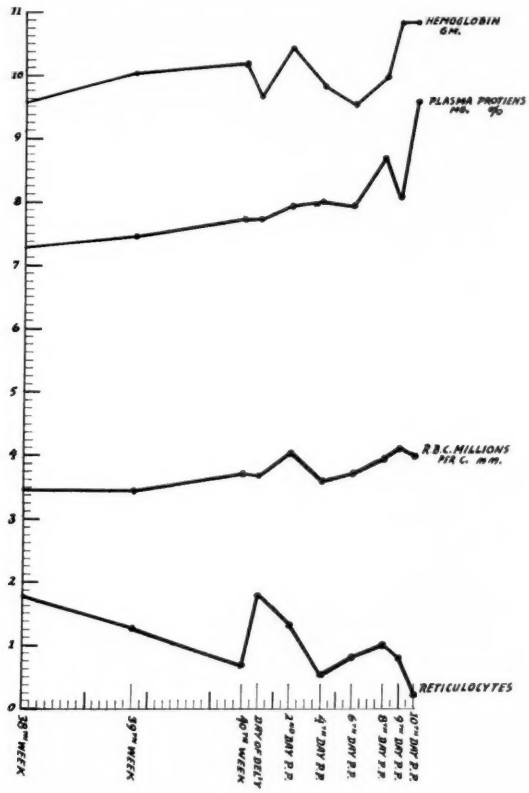

Fig. 1.

The cell volume following delivery continued to rise until the fourth day when a definite drop occurred. Thereafter the cell volume continued to show a steady increase until it rose to the normal level of 41 per cent on the tenth day post partum (Table II). Skajaa[10] found that in 14 women the cell volume increased steadily after delivery so that at from twelve to fourteen days it was normal at 43 per cent. The behavior of the cell volume in the puerperium probably represents the restoration of the normal physiologic relationship between the blood cells and blood plasma.

Although the cell volume rose to a normal level in the post-partum period, the mean corpuscular volume remained at a constantly high level, ranging between 100.6 and 104.1 cubic microns. This suggests that the higher value of the hematocrit is due, not to any alteration in the size of the individual red corpuscles, but to the greater number of packed cells per volume of blood. The amount of corpuscular hemoglobin remains unaltered. However, the mean corpuscular hemoglobin concentration is slightly below normal from the fourth to the eighth day post partum (Table II).

TABLE I. ANALYSES OF RED BLOOD COUNT, HEMOGLOBIN, HEMATOCRIT, PLASMA PROTEINS AND RETICULOCYTE COUNT IN THE LAST MONTH OF PREGNANCY AND PUERPERIUM ON 19 PREGNANT WOMEN

PERIOD OF GESTATION	RED BLOOD COUNT—MILLIONS PER C.MM.	HEMOGLOBIN GM. PER 100 C.C. BLOOD (SAHLI)	HEMATOCRIT %	PLASMA PROTEINS MG. PER 100 C.C. BLOOD	RETICULOCYTES
Thirty-eighth week	3.47	9.60	34.70	7.28	1.80
Thirty-ninth week	3.45	10.02	36.22	7.44	1.28
Fortieth week	3.70	10.16	37.07	7.71	0.66
Delivery day	3.66	9.63	38.25	7.72	1.80
Second day post partum	4.02	10.40	40.47	7.91	1.31
Fourth day post partum	3.58	9.83	36.90	7.98	0.53
Sixth day post partum	3.67	9.50	38.20	7.93	0.80
Eighth day post partum	3.89	9.92	39.90	8.69	1.00
Ninth day post partum	4.08	10.80	41.75	8.04	0.80
Tenth day post partum	3.94	10.80	41.00	9.56	0.20

TABLE II. ANALYSES OF THE HEMATOCRIT ON 19 NORMAL PREGNANT WOMEN IN THE LAST MONTH OF PREGNANCY AND PUERPERIUM

PERIOD OF GESTATION	HEMATOCRIT %	MEAN CORPUSCULAR VOLUME IN CUBIC MICRONS	MEAN CORPUSCULAR HEMOGLOBIN IN MICROMICROGRAMS	MEAN CORPUSCULAR HEMOGLOBIN CONCENTRATION %
Thirty-eighth week	34.70	100.00	24.40	27.60
Thirty-ninth week	36.22	104.9	29.00	27.60
Fortieth week	37.07	100.10	27.40	27.40
Delivery day	38.25	104.50	26.20	25.10
Second day post partum	40.47	100.60	25.80	25.70
Fourth day post partum	36.90	103.10	27.40	24.00
Sixth day post partum	38.20	104.10	25.80	24.80
Eighth day post partum	39.90	102.30	26.00	24.80
Ninth day post partum	41.75	102.30	26.40	25.80
Tenth day post partum	41.00	104.10	27.40	26.30

TABLE III. ANALYSES OF STUDIES ON THE RED BLOOD COUNT, HEMOGLOBIN AND HEMATOCRIT ON 44 NORMAL PREGNANT WOMEN

RANGE OF R.B.C.	AV. R.B.C.	RANGE OF HB	AV. HB	RANGE OF HEMA.* %	AV. HEMA. %	RANGE OF M.C.V.* C. μ	AV. M.C.V. C. μ	RANGE OF M.C.H.* MICRO.*	AV. M.C.H. MICRO.	RANGE OF M.C.H.C.* %	AV. M.C.H.C. %
3.89M.-4.96M.	4.25M.	11.0 gm.-14.55 gm.	12.23 gm.	32-45	38.9	74.4-109.3	89.59	23.91-37.00	29.25	25.3-37.17	31.36

*Hema., Hematocrit. M.C.V., Mean corpuscular volume. M.C.H., Mean corpuscular hemoglobin. M.C.H.C., Mean corpuscular hemoglobin concentration. Micro., Micromicrograms.

The plasma proteins were found to increase after delivery (Table I).

Normal values of the hematocrit have been reported variously. In the pregnant woman, Skajaa[10] gives 36.4 per cent as the average normal. Dieckmann and Wegner[5] report an average of 38.1 per cent between the thirty-sixth and fortieth weeks and 40.1 per cent between the tenth and twenty-fifth days post partum.

Wintrobe[13] found the range of the mean corpuscular volume in the nonpregnant woman to be 80 to 94 cubic microns, with an average of 87. In the pregnant woman Dieckmann and Wegner[5] determined the range of the mean corpuscular volume to be 80 to 100 cubic microns.

In order to determine normal values of cell volume and mean corpuscular volume for this study, hematocrits were obtained on 44 normal pregnant women. The range of the cell volume was found to be 32 to 45 per cent, with an average of 38.9 per cent. The range of the mean corpuscular volume was 74.4 to 109.3 cubic microns, with an average of 89.6 cubic microns (Table III).

DISCUSSION

The increase in plasma proteins and hematocrit in the post-partum period probably results because of the readjustment in blood volume which follows delivery. DeLee[3] and Williams[12] believe that the blood volume increases during pregnancy and decreases during the puerperium. Dieckmann and Wegner[4] also found that the plasma and blood volumes begin to increase in the first trimester of pregnancy, and at term there occurred an average increase of 23 per cent in blood volume and 25 per cent in plasma volume.

The increase in the plasma proteins, cell volume, and erythrocyte count in the puerperium without a rise in reticulocytes, suggests that hematopoiesis is not the factor producing the rise in the red blood count. Furthermore, the rapidity with which the increase in the erythrocyte count takes place favors the idea of concentration rather than hematopoietic activity. That the increase in the red blood count, in the puerperium, may be due to concentration, occurring as the result of fluid loss with subsequent readjustment of blood volume, is further suggested by the fact that during the period of observation prenatally, no noticeable rise in the erythrocyte count and hemoglobin could be obtained in a number of patients showing a mild form of anemia. In a recent study (Labate[7]), it was found that treatment with 1 gm. of ferrous sulfate daily caused an increase in the red blood count from an average of 3.63 million to 3.88 million, and in hemoglobin from an average of 9.54 gm. to 11.17 gm. It was impossible to produce any further increase above these levels, in spite of intensive treatment with ferrous sulfate, parenteral liver, and a high protein diet. Nineteen of these patients were under constant observation on the obstetric ward during this period of intensive therapy. In those instances where hypoacidity of the gastric juice was demonstrated, dilute HCl was given orally without any effect.

It is apparent, therefore, that the diminution in the red blood count and hemoglobin in many of the mild forms of anemia, seen during pregnancy, may be due to dilution resulting from an increase in blood volume. These, then, represent physiologic and not true anemias of pregnancy. Bethell[2] came to the conclusion that, with the hematocrit as a basis for calculation and on the assumption that there occurs no compensatory output of erythrocytes, the lowest red blood count that may be

explained solely by hydremia is approximately 3.7 million and the lowest hemoglobin about 11.3 gm. (70 per cent).

The true anemias of pregnancy were found to respond quickly to iron therapy. One gram of ferrous sulfate daily is an efficacious dose. With this form of therapy on 325 pregnant women, the average red blood count rose from 3.68 million in the prenatal period to 4.09 million at the time of delivery. The average hemoglobin rose from 9.56 gm. to 11.61 gm. (Labate[7]).

CONCLUSIONS

1. The erythrocyte count, hemoglobin cell volume, and plasma proteins show a definite rise during the first ten days following delivery. The reticulocyte count remains at a low level.
2. Whereas the red blood count rises to normal within the first ten days post partum, the hemoglobin remains 9 per cent below normal.
3. The cell volume also rises steadily in the puerperium to a normal of 41 per cent by the tenth day.
4. The increase in cell volume is not associated with any increase in mean corpuscular volume or mean corpuscular hemoglobin.
5. The plasma proteins rise steadily in the puerperium.
6. The increase in cell volume and plasma proteins and the rapid rise in the erythrocyte count in the post-partum period is due to concentration occurring as the result of fluid loss with consequent readjustment of blood volume.
7. Some of the mild forms of anemia developing during pregnancy are due to physiologic readjustments and do not represent true anemias.
8. The true anemias of pregnancy respond well to 1 gm. of ferrous sulfate daily.

REFERENCES

(1) *Barbour, Henry G., and Hamilton, William F.:* J. Biol. Chem. **69:** 625, 1926. (2) *Bethell, Frank H.:* J. A. M. A. **107:** 564, 1936. (3) *DeLee, J. B.:* Principles and Practice of Obstetrics, ed. 5, Philadelphia, 1928, W. B. Saunders Company, p. 105. (4) *Dieckmann, W. J., and Wegner, C. R.:* Arch. Int. Med. **53:** 71, 1934. (5) *Idem:* Ibid. **53:** 188, 1934. (6) *Heller, V. G., and Paul, Henry:* J. Lab. & Clin. Med. **19:** 777, 1934. (7) *Labate, John S.:* Am. J. Obst. & Gynec. **38:** 48, 1939. (8) *Idem:* Am. J. Obst. & Gynec. **38:** 650, 1939. (9) *Peters, J. P., and Van Slyke, D. D.:* Quantitative Clinical Chemistry, Baltimore, Vol. 1, 1931, and Vol. 2, 1932, Williams and Wilkins Company. (10) *Skajaa, K.:* Acta obst. et gynec., Scandinav. **8:** 371, 1929. (11) *Strauss, M. B.:* J. A. M. A. **102:** 281, 1934. (12) *Williams, J. W.:* Obstetrics, ed. 6, New York, 1930, D. Appleton-Century Company, p. 207. (13) *Wintrobe, M. M.:* J. Lab. & Clin. Med. **17:** 899, 1932.

Binet, A., and Canel, R.: Hypogastric Sympathectomy for a Case of Incurable Cancer of the Uterus, Bull. Soc. d'obst. et de gynée. **27:** 109, 1938.

A case of inoperable carcinoma of the uterus is reported in which the authors performed a hypogastric sympathectomy. The result was excellent even though there was an extension of the disease into the parametria. The authors believe that in some cases chemical sympathectomy will yield as good results as surgical sympathectomy.

J. P. Greenhill.

TRANSVERSE PRESENTATIONS

With a Report of 24 Cases Including One of "Conduplicato Corpore"

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AMONG about 20,000 labors, there were 24 patients with transverse presentation of the fetus, all delivering at term except 3 at eight months. Two others were recorded at seven months' premature labor that necessitated version and extraction. Thirteen of these were colored and 11 were white women. The population of this city here is 40 per cent negro and 60 per cent white. The incidence, therefore, is greater in the negro women than in the white, occurring once in 615 negro deliveries and once in 1090 white deliveries. The white people here are predominantly Anglo-Saxon. The records revealed that all were married. One white and one colored woman were pregnant with twins.

Age Incidence.—Eleven white women ranged from 18 to 34 years of age, 4 of these were from 20 to 25 years, and 4 were in the age group of 31 to 34 years. Thirteen colored women were from 20 to 40 years of age, 8 of whom were in the third decade.

Parity.—Only 2 were primiparas, one white woman 18 years old and one colored woman of 20. One white woman had had 10 children, one 6, and one 5. The others had one to three each.

Complications.—Prolapse of fetal hand and arm occurred in 13 cases; no prolapse in 11 cases. Five patients had hypertension, the highest blood pressure being 170/120 mm. Hg. Three patients had induction of labor by catheter insertion, 2 for hypertension and 1 for pyelitis. Five patients had albuminuria at time of labor, and 2 had pyelitis, 1 case of which developed after delivery.

LENGTH OF LABOR	MOTHER	FETUS L—LIVED D—DIED
0- 6 hr.	5 lived	D L L L D
6-12 hr.	8 lived	(Twins L D) L L (Twins L L) D D D D
12-18 hr.	3 lived	L L L
18-24 hr.	3 lived	L L D
24-36 hr.	1 lived	L
48 hr.	1 died	D
76 hr.	1 lived	L
"Long and exhausting"	1 lived	D
"Several days"	1 died	D

Management.—In general, nonneglected patients, in labor less than twenty-four hours, were treated by version and extraction after com-

plete dilatation of the cervix. Two of these had the cervix dilated by Voorhees' bag of large size, a procedure highly recommended. Forceps to the aftercoming head was used in 3 cases. With this treatment there were no maternal deaths, a low grade sepsis rate of 5 per cent, and a fetal mortality rate of 40 per cent. Five patients were considered neglected, i.e., in labor longer than twenty-four hours. Two of these were delivered by version and extraction. One of the mothers and her baby lived. The other one was a colored woman, 40 years old, in labor several days, with a fetal arm out and macerated. She was delivered by version and extraction through an incompletely dilated cervix, following which she went into surgical shock and died within twenty-four hours, probably from rupture of the lower uterine segment. Preliminary use of a large bag probably would have saved her life. Three patients were delivered, 2 by embryotomy (decapitation) and the third, spontaneously, by conduplicato corpore. The case records of these 3 are appended.

CASE 1.—A colored woman, medium to obese constitutional type, aged 29 years, para v, gravida vi, at term, entered the hospital from a long distance with history of labor of forty-eight hours' duration. She had transverse presentation of a 7 pound 14 ounce infant with prolapsed left arm and right foot, with the fetal head above the pelvic brim to the left. The body was wedged in the pelvis and there were no signs of life in the fetus. Treatment included decapitation of the fetus by Braun's hook method. Examination revealed no tears in the cervix or in the fundus. Nevertheless this method entails severe bruising trauma to the lower uterine segment. The time required for this operation by this method in this case was one hour, and in spite of postoperative blood transfusions, the patient developed sepsis, with chills on the second and third days, lasting twenty to twenty-five minutes each. On the twelfth day she developed pneumonia and died on the twenty-first day. From this experience an original set of instruments was devised to reduce the time and trauma in future instances of this kind, and the next case report illustrates the use.

CASE 2.—A colored multipara, of medium to obese constitutional type, aged 38 years, para viii, gravida ix, with all children living, entered the hospital from a distance. She was near term, pregnant with twins, the lower one apparently dead with macerated left hand and forearm at the vulva. The head was to the left and above the pelvic brim. The body was wedged into the pelvic inlet. The second baby was in good condition. She had been in labor ten hours. The treatment instituted was decapitation of the first twin by an original method as follows: The obstetrician's left hand could be inserted into the cleansed and draped vagina far enough to get the index finger partly around the dead child's neck. A sterile 18-inch length of lead tubing, outside diameter ¼ inch, inside diameter ⅛ inch, was inserted underneath the finger which bent it to conform to the cervical curvature. As the pliable tubing was inserted farther the upper curved end returned on the lower side of the neck. It was a simple matter to replace the lead tube with No. 13 piano wire which was then used as a snare through a brass tube and the head neatly and quickly severed from the body, leaving no jagged points of bone. The body then was easily removed, as was the head which was somewhat macerated. The live twin then was turned by the feet and extracted. Examination revealed a 2 cm. lateral laceration of the cervix which was sutured with catgut.

The time of anesthesia by cyclopropane was thirty minutes. The mother and the second child recovered and went home on the seventh day. While this patient was not in the desperate condition of the one reported above, the difference in time required for the two operations, the difference in trauma, and the variation in facility of performance are much in favor of this procedure.

CASE 3.—A colored woman, aged 24 years, para ii, gravida iii, attended the prenatal clinic once or twice. She went into labor on about the date calculated from her last menstrual period, and she was delivered in her home by the student obstetricians. The first stage of labor lasted eight hours and ten minutes, at the end of which time the membranes ruptured spontaneously and a male fetus weighing 3,118 gm., macerated, and so much softened that the bones felt like beans in a bean bag, was delivered in fifteen minutes. The report of the delivery stated that the "Right shoulder delivered first, the head to the left, and completely flexed on the chest, followed, then the left shoulder, these came out at a slight angle deviating somewhat to the mother's right. The trunk followed immediately with the legs, which were extended. The arms were along the sides of the body. The birth occurred very rapidly after the shoulders came down, all of the fetus coming out with one pain very much as a half congealed jelly might be poured out of a container. The head was so macerated and flexed that the three of us thought for a moment that no head existed. The cord was blue black, twisted, and around the fetus' neck. The placenta was seen to be lying in the vaginal orifice and fell out easily when touched. It was necrotic. The fetus had been dead about two weeks. The mother was in very good condition and made an uneventful recovery."

The placenta weighed 569 gm. The mother's blood was Wassermann negative, her urine was normal, and the blood pressure was normal until after probable death of the fetus, then 150/80.

SUMMARY AND COMMENT

In this study transverse presentation at term and in labor occurs once in about 615 negro deliveries and once in 1,090 white deliveries, with an incidence ratio in negro and Anglo-Saxon women of 10 to 6. There is a high incidence in multiparas and in twin pregnancies.

An arm prolapsed is found in about 55 per cent of cases. If in labor more than twenty-four hours, a patient so afflicted may be considered neglected.

The usual and very successful treatment in nonneglected patients is version and extraction after complete dilatation of the cervix. An original method of fetal decapitation in neglected patients is described. In order to be certain of how the baby lies, an x-ray study should be made before operation. In the nonneglected patients, the maternal mortality is negligible with low sepsis rate. The fetal mortality is about 40 per cent. Both mortality rates rise rapidly in the neglected patients.

Benthin, W.: Prontosil for the Treatment of Septic Conditions in Gynecology, Med. Klin. **34:** 1347 and 1490, 1938.

Benthin is skeptical about the benefit of prontosil in cases of sepsis but he is enthusiastic about the value of this drug in cases of puerperal and postabortal endometritis. He is in favor of using prontosil prophylactically in all febrile puerperal conditions and in all cases where there appears to be a threatened infection. The drug should be given early. Prontosil is the best drug of its group and is the least dangerous. The drug may be given rectally, hence can prevent the giving of painful injections.

In spite of the use of prontosil, every known means of treating puerperal infections should be employed at the same time.

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PATHOLOGIC AND CLINICAL ASPECTS OF ADENOMYOSIS AND ENDOMETRIOSIS

A Survey of 224 Cases

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ADENOMYOSIS and endometriosis† have been the object of numerous investigations. Many points are, nevertheless, still controversial. It seemed, therefore, worth while to report the data of 224 specimens which were examined in this laboratory during a period of almost ten years.

It is not my purpose to discuss the various theories concerning the genesis of adenomyosis and endometriosis. I shall rather confine myself to a report of the figures and facts and to an attempt at interpreting them as far as they permit.

INCIDENCE AND LOCALIZATION

From 1930 to 1939 approximately 16,000 surgical specimens were examined. Among them were 1,807 uteri which presented the following principal lesions:

	NO. OF CASES		NO. OF CASES
Myomas	1424	Benign tumors (except myoma)	13
Hyperplasia of myometrium	238	Metastatic carcinoma	3
Prolapse	88	Sarcoma	3
Carcinoma of body of uterus	37	Chorionepithelioma	1

Adenomyosis and endometriosis were found in 224 instances or in 12.4 per cent of the extirpated uteri.

The localization of the lesions was as follows:

Myometrium	152	Broad ligament	1
Ovary	41	Serosa of appendix	2
Tubal angles	12	Abdominal scar	1
Serosa of uterus	7	Bladder	1
Pelvic serosa	6	Round ligament (extraperitoneal)	1
			224

Adenomyosis, therefore, represented almost 70 per cent of the cases. The same incidence was reported by Frankl and Counsellor, whereas Jeffcoate, Seitz, and others stated a higher percentage of endometriosis. They probably paid more attention to endometriosis on account of its greater clinical significance. Furthermore, the criteria for diagnosing ovarian endometriosis are not uniform (King). Adopting the criteria used by Seitz the incidence of ovarian endometriosis would almost be doubled.

Among 380 autopsies of women between 20 and 55 years of age, 2 cases of adenomyosis and 1 case of endometriosis were found.

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†The terminology proposed by O. Frankl has been adopted. "Adenomyosis" designates the invasion of the myometrium by cytogenic tissue and endometrial glands from within the uterus; "endometriosis" means the presence of endometrium-like structures outside the uterus or invading the uterus from without.

AGE DISTRIBUTION

Adenomyosis: (152 cases)

	21-30	31-40	41-50	51-60	61-
No.	3	40	96	12	1
Per cent	2	26	63	8	

Six women, or 4 per cent, were under 35 years of age, 96 per cent were older than 35, and 72 per cent were older than 40 years. The average age was 46, the mean age 44; the youngest patient was 24, the oldest 63 years.

Ovarian endometriosis: (41 cases)

	21-30	31-40	41-50	51-
No.	12	22	6	1

Thirty per cent were under 30, 54 per cent were under 35 years of age, 19 per cent were older than 40. The average age was 33, the mean age 36; the oldest patient was 57, the youngest 22.

The difference in age incidence is evident. While adenomyosis belongs definitely in the second half of the generative period, endometriosis occurs in women at the height of their sex life.

The adenomyotic structures were of the "resting" type in the patients who were not menstruating any more. In these cases no histolysis was present. This may be ascribed to the decrease in ovarian function connected with the menopause.

An attempt was made to correlate the severity of the lesions with the age of the patient. The invasion of the myometrium was slight in 44 per cent of the women under 40, but only in 24 per cent of the patients between 40 and 50, and in only one case in a woman over 50. These figures demonstrate that adenomyosis is a progressive lesion and that it starts after 35 years of age in most instances.

These differences in age distribution point clearly to a different mechanism in adenomyosis and endometriosis.

COMBINATION OF ADENOMYOSIS AND ENDOMETRIOSIS

Adenomyosis was combined with ovarian endometriosis three times and with other forms of endometriosis in three instances also. This rarity of the combination is another factor in suggesting a different origin.

COMBINATION WITH OTHER PELVIC DISEASES

Adenomyosis was found together with myomas in 61 cases; with hyperplasia of the myometrium in 44 instances, and with myomas plus hyperplasia in 40 cases. There was postmenopausal atrophy of the uterus in 7 instances. A normal myometrium was found in not a single case. (A myometrium more than 2 cm. thick was considered hyperplastic.)

Endometriosis of the ovary was combined with myomas in 70 per cent of all cases.

Microcystic ovaries were present in 25 instances. This figure, however, may not be correct, because in cases in which only a hysterectomy was done, the data relative to the ovaries were sometimes not complete.

Adhesions were present in more than 50 per cent of the cases.

The high incidence of myomas is a universal feature of all statistics on adenomyosis and endometriosis.[8, 9, 17] Vice versa, in about one-seventh of the myoma patients, adenomyosis or endometriosis was found. This is by far more than the probable incidence. It has led Seitz and others to assume a common origin for these lesions. The investigations of Jeffcoate and Lipschuetz tend to support this point of view.

All uteri which were not myomatous had a hyperplastic myometrium. Hyperplasia of the myometrium is usually found in multiparous women (Adler). This fact also strongly suggests a common factor in the genesis of hyperplasia of the myometrium and of adenomyosis.

Several authors have postulated a constitutional factor in the etiology of adenomyosis and endometriosis. As a possible indicator of some primary constitutional

deviation, the original menstrual history of the patient was studied. Only 26 out of 152 patients with adenomyosis had originally an abnormal menstrual cycle. In all the other cases the menstruation was originally "normal." Of the 41 patients with endometriosis of the ovaries, only 7 had originally disturbed menstruation. The first menstruation occurred at the normal age in these patients. It was not delayed, as Frankl noticed in his cases.

CARCINOMA AND ADENOMYOSIS OR ENDOMETRIOSIS

The possibility of carcinomatous degeneration seems very likely indeed if one considers the histolytic and hyperplastic activity of adenomyosis and endometriosis. However, only isolated cases[6, 17] have been reported. None of them has withstood R. Meyer's criticism. One of the two cases in our material was highly suggestive of carcinomatous change in adenomyotic lesions. No definite proof was possible.

Almost as rare is the coincidence of cancer and endometriosis.[23]

STERILITY AND FERTILITY

In 140 cases of adenomyosis the distribution was the following:

STERILE	ABORTIONS ONLY	1 PARA	MULTIPARA	UNMARRIED OR CONTRACEPTIVES	NO DATA
4	4	4	109	10	9
3%	3%	3%	78%	7%	6%

In 41 cases of ovarian endometriosis:

STERILE	ABORTIONS ONLY	1 PARA	MULTIPARA	UNMARRIED OR CONTRACEPTIVES	NO DATA
13	4	3	10	7	4

Of 18 patients with endometriosis (ovary excluded), 3 were sterile, 2 had abortions only, 4 were unmarried, and the others had 1 or more children.

Almost 50 per cent of the patients with adenomyosis had had more pregnancies than deliveries. Among the women with ovarian endometriosis only 4 gave a history of interrupted pregnancies.

The very low sterility index of adenomyosis was surprising. For comparison, two statistically suitable groups, each of 200 patients, were taken. The number of sterile patients in these groups was 10 per cent and 9 per cent, respectively. This is twice the incidence found in patients with adenomyosis. The percentage of women with abortions only was the same in the two control groups as in adenomyosis. There was, however, a remarkable difference in the number of childbirths. In the control group, 15 per cent and 24 per cent, respectively, had one child only, of the patients with adenomyosis but 4 per cent. On the other hand, the multiparas represented about 50 per cent of the control group and almost 80 per cent in adenomyosis. These figures highly suggest a possible role of repeated childbirth or abortions in the genesis of adenomyosis. The experimental production of adenomyosis by curetting the pregnant uterus tends to corroborate this assumption.[24]

The high sterility index in ovarian endometriosis has been stated universally.[3, 8, 22] Turunen frequently noticed hypoplasia of the sex organs in his patients. I was unable to verify his observation in our material.

Most statistics report previous pelvic or abdominal operations in up to 50 per cent of the cases with ovarian endometriosis. Only 6 of our 41 patients, however, had been operated upon previously. I do not know how to account for this difference.

FUNCTIONAL CHANGES IN ENDOMETRIUM AND IN ADENOMYOSIS

Lack of space does not permit a discussion in detail of this interesting problem. The functional phase was found to be the same in the endometrium and in the adenomyotic structures in more than 50 per cent of the cases. In the majority of cases, the endometrium exhibited a normal picture corresponding to the phase of

the menstrual cycle. Glandular hyperplasia was present in only 13 per cent. The endometrium, therefore, does not give any evidence of ovarian dysfunction in the great majority of the cases.

SYMPTOMATOLOGY

Due to the frequent combination of adenomyosis with other pelvic disease, it is difficult to distinguish symptoms that are characteristic of adenomyosis. Excessive menstruation, with shortened interval, is considered the most important symptom.[1, 4, 19] However myomas as well as hyperplasia of the myometrium may cause similar symptoms. Jeffcoate, on the other hand, found metrorrhagia in 20 of his 26 cases.

In the present material, 92 of 138 patients complained of excessive bleeding. Fifty-four had hypermenorrhea, 27 polyhypermenorrhea, 4 had polymenorrhea, 4 had metrorrhagia. In many instances, however, the bleeding had become continuous for the last few weeks. No type of bleeding was found specific for myomas, myometrial hyperplasia, or adenomyosis.

Pain was complained of in 41 instances. It was dysmenorrheic in 16 patients, unrelated to menstruation and appearing as lower abdominal or back pain in 35 instances. The latter type was much more frequent in uncomplicated myometrial hyperplasia. Vaginal discharge, urinary disturbances and swelling of the abdomen were infrequent complaints.

Thirty-five of 41 patients with ovarian endometriosis complained chiefly of pain. Nineteen had dysmenorrhea of the acquired type, 16 had lower abdominal pain or backache unrelated to menstruation. Ten of the latter group had dysmenorrhea also. Thus, 29 altogether mentioned dysmenorrhea as chief complaint. This fact has been brought out by all authors. Uterine bleeding was present in 26 of these patients. It was menorrhagic in 24 instances; only 2 patients had metrorrhagia. As myomas were present in more than two-thirds of the cases, it remains doubtful what role the endometriosis played in the bleeding.

CONCLUSIONS AND SUMMARY

One hundred and sixty-four cases of adenomyosis uteri and 60 cases of endometriosis have been studied.

Adenomyosis, in our material, is almost 3 times as frequent as is endometriosis.

Adenomyosis belongs to the second half of the generative period. Multiparity seems to be one causative factor. The sterility index is lower than normal.

In no case of adenomyosis was the myometrium found normal; either myomas or diffuse hyperplasia of the myometrium, or both, were present. This seems to point to a common, possibly hormonal, etiologic factor.

Glandular hyperplasia was found only in one-eighth of the cases of adenomyosis. In about 50 per cent, the adenomyotic glands presented a picture similar to those of the endometrium. Absence of histolysis indicates inactivity of the adenomyotic process.

Persistent hypermenorrhea with dysmenorrhea in multiparous women between 35 and 50 years of age may be considered suggestive of adenomyosis. The frequent combination with other uterine diseases renders the preoperative diagnosis difficult.

Ovarian endometriosis occurs in younger women between 25 and 40 years of age, usually. Primary and secondary sterility are frequent. In 70 per cent of the cases myomas were present. Gynecologic operations have been carried out previously in a few cases only.

The menstrual cycle has been originally normal in the majority of women with adenomyosis and endometriosis.

The two conditions are found together only rarely. They probably represent two different processes with some factors in common.

REFERENCES

(1) *Adler, L.:* In Halban-Seitz: Biologie und Pathologie des Weibes **4:** 160, 1928. (2) *Albrecht, H.:* In Halban-Seitz: Biologie und Pathologie des Weibes **4:** 269, 1928. (3) *Cattell, R. B., and Swinton, N. W.:* New England J. Med. **214:** 341, 1936. (4) *Counsellor, V. S.:* Am. J. Obst. & Gynec. **36:** 877, 1938. (5) *Dougal, D.:* Tr. Edinburgh Obst. Soc., p. 61, 1937-1938; Am. J. Obst. & Gynec. **35:** 373, 1938. (6) *Frankl, O.:* Zentralbl. f. Gynäk. **56:** 902, 1932; Ztschr. Geburtsh. & Gynäk. **115:** 1, 1937. (7) *Jeffcoate, T. N. A., and Potter, A. L.:* J. Obst. & Gynaec. Brit. Emp. **41:** 684, 1934. (8) *Keene, F. E., and Kimbrough, R. A., Jr.:* J. A. M. A. **95:** 1164, 1930. (9) *King, E. S. J.:* Surg. Gynec. Obst. **53:** 22, 1931. (10) *Lipschuetz, A., and Vargas, L.:* Lancet **236:** 1313, 1939. (11) *Masson, J. C.:* Ann. Surg. **102:** 919, 1935. (12) *Meyer, R.:* In Veit-Stoeckel: Handbuch der Gynaekologie **6:** Part 1, 356, 1930; In Hencke-Lubarsch: Handbuch der path. Anat. **7:** Part 1, 249, 1930. (13) *Morris, J. W.:* South. Med. & Surg. **100:** 320, 1938. (14) *Novak, E.:* Am. J. Obst. & Gynec. **22:** 826, 1931. (15) *Nylander, P. E. A.:* Zentralbl. f. Chir. **65:** 75, 1938. (16) *Pemberton, F. A.:* New England J. Med. **217:** 1, 1937. (17) *Rockstroh, H.:* Zentralbl. f. Gynäk. **60:** 550, 1936. (18) *Sampson, J. A.:* Am. J. Obst. & Gynec. **24:** 497, 1932. (19) *Seitz, L.:* Arch. f. Gynäk. **149:** 529, 1932. (20) *Skamnakis, S. N.:* Zentralbl. f. Gynäk. **62:** 414, 1938. (21) *Smith, G. V. S.:* Am. J. Obst. & Gynec. **17:** 806, 1929. (22) *Turunen, A.:* Acta obst. et gynec. Scandinav. **18:** 237, 1938. (23) *Tuthill, R. C.:* Arch. Surg. **37:** 554, 1938. (24) *Zaleski, W.:* Zentralbl. f. Gynäk. **60:** 1046, 1936.

AN ATTEMPT TO CONTROL FETAL WEIGHT

Preliminary Report

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EXCLUDING prematurity, most neonatal deaths occur in babies having a birth weight in excess of eight pounds (3,636 gm.). As the fetal birth weight curve rises above eight pounds (3,636 gm.) both the fetal mortality and maternal morbidity curves also rise. The relationship between maternal and fetal weight curves has never been clearly established; however, it is known that the two curves often fail to coincide, because there are factors which cause elevation of maternal weight without affecting fetal weight, the most common factor being edema.

Practically speaking, the maternal weight curve is followed throughout pregnancy to reveal early evidence of toxemia, as manifested by edema. Clinical investigation has proved that maternal weight can usually be controlled by dietary restrictions; however, these restrictions have no effect upon fetal weight.

Realizing that maternal dietary excesses do not cause fetal obesity, the most reasonable etiologic factor that presents itself is a disturbance in thyroid metabolism. Williams[1] states that hypertrophy of the thyroid can be recognized clinically in 65 to 90 per cent of all pregnant women. Before an organ undergoes hypertrophy there must first be an increased demand placed upon that organ. In the case of preg-

nancy this increased demand is probably due to the presence of the fetus in utero. If the organ is unable to meet this demand by hypertrophy and hyperplasia, a state of deficiency or decompensation develops. One of the manifestations of thyroid deficiency is, of course, obesity.

Patterson, Hunt, and Nicodemus[2] demonstrated that in subclinical hypothyroidism during pregnancy the mother absorbs thyroxin from the fetus, producing fetal hypothyroidism. The fetal thyroid then reacts to this drain by undergoing extreme hyperplasia and hypertrophy. This leads to permanent damage to the gland with subsequent clinical thyroid disease later in life, dependent, of course, upon iodine supply and physiologic demands. Anselmino and Hoffman[3] reported a marked increase in the amount of thyroid hormone in the circulating blood of the mother during pregnancy; the amount increases as gestation progresses. The average amount of thyroxin found in the blood during pregnancy is twenty units to the cubic centimeter, according to these observers. Soule[4] substantiated the findings of Anselmino and Hoffman and expressed the belief that the increase in thyroid hormone is due to an actual physiologic hyperfunction of the thyroid gland during pregnancy. Williams[1] believes that thyroid deficiency results in a defective germ plasm and premature termination of pregnancy; if pregnancy continues, monstrosities result. Breckenridge[5] reports abortion, premature labor, and fetal death caused by thyroid insufficiency; his report includes 25 cases in which there was complete relief following thyroid medication.

With the foregoing evidence as a foundation, a series of cases was started, based upon the thesis that fetal obesity is due to a fetal thyroid deficiency which can be corrected by placing a sufficient saturation of thyroid extract in the fetal blood stream. One hundred and sixteen women have been given thyroid extract orally during four or more months of their pregnancies. Patients receiving less than four months of continuous treatment have not been included in this series. Each patient received not less than 3 gr. (0.2 gm.) and not more than 6 gr. (0.4 gm.) daily. Armour's enteric coated 1 gr. (0.065 gm.) tablets were used on all cases. These patients received no other medication that could influence weight and they were told to eat a normal, well-balanced diet without qualitative or quantitative food restriction. They were given no extradietary calcium or vitamins.

These women were seen at intervals of not less than two weeks at which time routine prenatal care was given; in addition, they were carefully examined for evidence of hyperthyroidism. The fact that these signs failed to develop in a single case is significant and further proves clinically that there is a thyroid deficiency during pregnancy; if 116 normal, nonpregnant women would be given from 3 to 6 gr. (0.2 to 0.4 gm.) of potent thyroid extract daily over a period of four or more months many of them would develop signs of hyperthyroidism.

Brown[6, 7] made two very comprehensive reports on the administration of thyroid extract during pregnancy; he was one of the first workers to discover the extreme variability of potency of the various thyroid preparations on the market. Davis[8] agrees with Brown; he advises selecting a single product of known high potency and giving it continuously to all patients throughout pregnancy. He further advises beginning the administration of thyroid extract prior to the pregnancy to avoid abortions and fetal maldevelopments. Mussey and Haines[9] advise giving a standard

brand of desiccated thyroid in doses of about 4 gr. (0.24 gm.) daily for three or four days and then dropping to a maintenance dose of 1 to 2 gr. (0.065 to 0.12 gm.) daily.

Basal rates were done on the first 56 cases; the average rate of this group at an average time of four months' gestation was plus 2 per cent; the average rate after three months of treatment was plus 22 per cent. Basal rates were discontinued when it was discovered that an elevated rate is normal during the latter half of pregnancy.

Williams[1] states that there is a definite elevation in the basal metabolic rate during the latter half of pregnancy, due to the presence of the fetus in utero. It returns to normal about the tenth post-partum day. Sandiford and Wheeler[10] found that the state of pregnancy demands increased secretion of thyroid extract because of the presence of an increasing mass of active protoplasmic tissue, consisting largely of the fetal tissues and partly of an increase in maternal structures incident to pregnancy. They found no change in the basal rate in the early months of pregnancy, but found a distinct rise to plus 20 or plus 25 per cent in the final trimester. Mussey, Plummer, and Boothby[11] found that basal rates of plus 25 to plus 30 per cent during the latter half of pregnancy do not necessarily indicate the presence of hyperthyroidism. Davis[8] pointed out the fact that basal rates in pregnancy are confusing and fail to give a true picture of thyroid function. He believes that a clinical test with the administration of desiccated thyroid is the only method which can be accepted at present. From the foregoing evidence it was concluded that thyroid deficiency can exist during pregnancy despite the presence of a normal basal rate.

The average maternal weight gain during entire pregnancy in this group of 116 cases was 18.2 pounds (8.3 kilograms). The average fetal birth weight was 6.8 pounds (3,090 gm.). There was no fetal mortality or prematurity and no maternal mortality. These weights are not spectacular but they are fairly satisfactory since there were no qualitative or quantitative food restrictions. The most gratifying point in this series is the fact that no baby weighed more than 7 pounds 12 ounces (3,522 gm.) and none less than 5 pounds 11 ounces (2,590 gm.).

Because of the small size of these babies and the fact that no more than 6 gr. (0.4 gm.) of nembutal were used for analgesia in a single case, it was necessary to apply forceps in only twelve instances. Eleven of these were applied below the spines and one in the midplane; this was the largest baby in the group and weighed 7 pounds 12 ounces (3,522 gm.); the mother had a justominor pelvis with an anteroposterior diameter of 10 cm. and a biischial diameter of 8 cm.

It has been suggested recently that thyroid deficiency might play some part in the etiology of the toxemias of pregnancy. Patterson, Hunt, and Nicodemus[12] demonstrated both clinically and experimentally that the increased metabolism of pregnancy produces a subclinical hypothyroidism, which is accompanied by hypercholesteremia. When the maternal thyroid cannot produce sufficient thyroxin the fetal thyroid is drained; this constant depletion of fetal thyroxin produces a fetal hypothyroidism and hypercholesteremia. Fetal hypercholesteremia causes the deposition of cholesterin in the walls of the placental arteries, producing an endarteritis. If the endarteritis is severe, the arterial lumen will be occluded, resulting in placental infarction and

degeneration. Toxins absorbed from this degenerating placental tissue produce clinical eclampsia with convulsions in the mother. In this group it is of passing interest that there were no cases of eclampsia or pre-eclampsia.

SUMMARY

One hundred and sixteen women were given daily doses of from 3 to 6 gr. (0.2 to 0.4 gm.) of desiccated thyroid extract during four or more months of their pregnancies without qualitative or quantitative food restrictions. One hundred and sixteen normal babies having an average birth weight of 6.8 pounds (3,090 gm.) were delivered. The mothers demonstrated no signs of hyperthyroidism, pre-eclampsia, or eclampsia, and they gained an average of 18.2 pounds (8.3 kilograms) during their pregnancies.

CONCLUSIONS

This series is too small to reach any final decision regarding the merits of this treatment; however, the results to date are encouraging and merit further study by those who might be interested.

REFERENCES

(1) *Williams, J. W.:* Obstetrics, ed. 7, New York, 1936, D. Appleton-Century Co., p. 225. (2) *Patterson, W. B., Hunt, H. F., and Nicodemus, R. E.:* West. J. Surg. **44:** 486, 1937. (3) *Anselmino, K., and Hoffman, F.:* Arch. f. Gynäk. **143:** 310, 1930. (4) *Soule, S. D.:* Am. J. Obst. & Gynec. **23:** 165, 1932. (5) *Breckenridge, S. D.:* Ibid. **23:** 871, 1932. (6) *Brown, C. F.:* Texas State J. Med. **26:** 406, 1930. (7) *Brown, C. F.:* Ibid. **31:** 287, 1935. (8) *Davis, C. H.:* Am. J. Obst. & Gynec. **30:** 570, 1935. (9) *Mussey, R. D., and Haines, S. F.:* Ibid. **27:** 404, 1934. (10) *Sandiford, Irene, and Wheeler, Theodora:* J. Biol. Chem. **62:** 329, 1924. (11) *Mussey, R. D., Plummer, W. A., and Boothby, W. M.:* J. A. M. A. **87:** 1009, 1926. (12) *Patterson, W. B., Hunt, H. F., and Nicodemus, R. E.:* Am. J. Clin. Path. **8:** 120, 1938.

TREATMENT OF METROMENORRHAGIA WITH TESTOSTERONE PROPIONATE

A Preliminary Report

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THE purpose of this report is to present our experiences with the use of testosterone propionate in the treatment of metromenorrhagia. Here we are particularly concerned with the average minimal dosage necessary to control the excessive bleeding.

The therapeutic rationale for the use of testosterone propionate will be fully reviewed elsewhere.[1] Briefly summarized, the following considerations appear pertinent. The effects of testosterone on the endometrium are variable. A progestational response may be elicited, for example, in the rabbit,[2] but apparently not in the monkey[3] or human being.[4] Hypoplasia of the endometrium may result from chronic in-

jections of testosterone,[5] but this may occur similarly with estrone.[6] On the other hand the response of the myometrium seems fairly clear. Estrone will initiate and maintain rhythmic, intermittent contractility. Testosterone will inhibit this.[7] Since the myometrium plays such an essential role in controlling the volume flow of blood to the endometrium,[8, 9] the effect of testosterone on it becomes the more significant. Because intermittent, rhythmic motility is inhibited, the volume flow of blood *to* the uterus is lessened.[10] By reason of its direct squeezing action on the myometrial elements,[1] the volume flow of blood *in* the myometrium is reduced. The end result will be a reduction in the flow of blood to the endometrium, and thus, a diminution in the amount of uterine bleeding.

MATERIAL

On the basis outlined above, and remembering the well-known clinical fact that patients with arrhenoblastomas experience first a diminution and then a cessation of menses, we began more than a year ago to observe and treat patients with metromenorrhagia with testosterone propionate. Some were carefully followed for some months before being treated. Since the immediate treatment of the bleeding is the primary concern of this report, we have selected 14 typical cases. All but 2 have had at least 1 previous dilatation and curettage. Their ages ranged from 15 to 48 years.

Endometrial findings were as follows: hyperplasia, 6; secretory, 3; interval, nonsecretory, 7; and chronic endometritis, 1. This makes a total of 17, because 3 patients presented a different type of endometrium on separate occasions of profuse bleeding. One showed hyperplasia on 2 occasions and an interval, nonsecretory phase on another. Two showed a secretory endometrium at one time and an interval, nonsecretory picture on a subsequent curettage. A previous history of pelvic inflammatory disease was given by 4, of which 2 had endometrial hyperplasia; 1 an interval, nonsecretory endometrium, and 1, chronic endometritis. Two dated their excessive bleeding from parturition; 1 had hyperplasia, and the other showed a secretory endometrium on one occasion and an interval, nonsecretory picture subsequently. There were 2 cases of puberty menorrhagia, both hyperplasia; and 3 premenopausal, 1 hyperplasia, and 2 interval, nonsecretory.

DOSAGE

The dosage employed at any one time ranged from 5 to 25 mg. of testosterone propionate. The usual dose was 10 mg. Where the bleeding was active and quite profuse, the first dose was given either intramuscularly or else divided between the intramuscular and subcutaneous routes, the subsequent injections being given subcutaneously. When given by the latter route, the hormone was injected deep enough so that no swelling was apparent in the skin over the deltoid region. An intravenous needle was used.

The interval between injections varied from two to four days. As a rule 2 to 4 injections were sufficient. The average minimal dosage necessary to lessen bleeding materially was 10 to 30 mg. The total dosage required to stop the flow completely varied from 10 to 120 mg., with an average of 40 to 60 mg.

The elapsed time before a therapeutic result was obvious varied from twelve hours to four days. Usually there was a sharp diminution in bleeding within forty-eight hours.

When used prophylactically, the dosage varies somewhat with the type of endometrium found premenstrually. In cases with a secretory or an interval, nonsecretory picture, a total of 10 to 30 mg. of testosterone propionate given in divided doses, subcutaneously, in the seven to ten days before the expected period is usually sufficient to control the succeeding period. In cases of hyperplasia, 50 to 100 mg. given in divided subcutaneous doses during the last two or three weeks of the cycle usually check the tendency to excessive flow.

The following case histories briefly illustrate the method of approach:

CASE 1.—Patient, aged 39 years, had suffered with menorrhagia since parturition in 1936. A dilatation and curettage in 1937 revealed endometrial hyperplasia. She was seen on the eighteenth day of a profuse flow saturating 12 to 15 napkins daily. She was given 25 mg. of testosterone propionate intramuscularly. Two days later, the flow having abated considerably after a slight initial exacerbation the first night, she was given a similar dose. This was repeated twice. Total dosage was 100 mg. Two months later, she reported to the dispensary on the thirteenth day of another profuse flow. She was given 20 mg. of testosterone propionate subcutaneously and a similar dose was repeated six days later, the flow having become a dribble two days after the first injection. After that she was given 20 mg. subcutaneously twice a week for two weeks more. Since then (six months) her periods have been normal in duration and amount. It is to be noted that it required 100 mg. intramuscularly to stop the flow in five days while it required 40 mg. subcutaneously to stop it in eight days under essentially similar conditions.

CASE 2.—Patient, aged 29 years, had required a curettage for excessive menses twice in 1937. Both disclosed endometrial hyperplasia. Periods, however, continued to be profuse. Endometrial biopsy on the twenty-eighth day of the cycle revealed a very well-developed proliferative endometrium diagnosed as a questionable hyperplasia. She was given 30 mg. (3 × 10) in the next five days and then the period started as profuse as usual. She was given 10 mg. on the third day with no relief. On the sixth day, she was given 20 mg. intramuscularly. After an initial gush, the flow abruptly ceased that night. Sixty milligrams of testosterone propionate merely decreased the duration but not the amount of flow. Suction biopsy on the seventeenth day of the next cycle revealed an interval, nonsecretory endometrium. Starting on the twentieth day of the cycle she received 100 mg. of testosterone propionate in divided subcutaneous doses over the course of the next ten days. Suction biopsy on the thirty-first day revealed a secretory endometrium. Her period began on the thirty-fourth day, lasted four days, and was normal in amount. The finding of a secretory picture is probably explainable on the gonadotropic action of testosterone.[16] Suction biopsy two months later still showed a secretory endometrium premenstrually. When again seen six months later her only complaint was that she had still not regained her "nature" (libido), which had disappeared after the first series of injections. Her periods have continued to remain normal in duration and in amount.

CASE 3.—Patient, aged 23 years, colored housewife, had pelvic inflammatory disease in 1934. In the past two years she developed severe dysmenorrhea and polymenorrhea with profuse flow. For the past six months she complained of intermenstrual spotting. Pelvic examination revealed a normal but fixed, anteflexed uterus. Endometrial biopsy on the day before her expected period disclosed an interval, nonsecretory picture. She was given 20 mg. (4 × 5) in the next eight days. Menses set in on the ninth day without pain, and was moderately profuse, requiring 7 to 8 pads daily instead of the usual 15 to 20 pads. Flow tapered off on the fifth day. However, it re-appeared on the seventh day along with menstrual cramps. Accordingly she was given 10 mg. intramuscularly. Following an increase of the flow that evening, menses stopped the next day. Endometrial biopsy a few months later showed a secretory picture premenstrually. Periods were normal in type, duration and amount (2 to 4 pads daily), while her dysmenorrhea had disappeared.

CASE 4.—This case illustrates the excellent results obtained in cases of cyclic menorrhagia from a secretory endometrium. Patient, aged 23 years, had cyclic menorrhagia for past seven years. Flow accompanied by clots, lasted nine to eleven days requiring 8 to 10 pads daily. Endometrial biopsy revealed a secretory phase premenstrually. She was given 15 mg. (3 × 5) in divided subcutaneous doses in the week before her period. Flow lasted but five days, contained no clots, and was normal in amount. Since then, with no further therapy, periods have been normal in duration and amount (six months).

ANALYSIS OF RESULTS

Relatively small amounts (10 to 30 mg.) of testosterone propionate are required to lessen the bleeding materially, i.e., reduce the flow to a dribble. A somewhat larger amount is required to stop the bleeding completely. The dosage schedule employed stands in marked contrast to that of others[11] who recommended dosages of two hundred to two thousand mg. However, while this paper was being prepared, Beclere[12] reported that very moderate doses were needed (25 to 50 mg.) to control excessive bleeding. On the basis of the calculations of Kenyon[13] it is felt that single doses of 5 to 25 mg. are within physiologic limits. A phenomenon that may explain the large dosages used by the workers quoted above is, that quite frequently, following a slight immediate reduction in flow, there may occur a more or less marked exacerbation of flow which may last from three to twelve hours or more. Injections of testosterone propionate should not be given at this point, for the increased flow may be extended over a still longer period of time. (In one case, not reported here, it lasted five days.) This transient increase of flow is almost pathognomonic of a subsequent sharp decrease and rapid cessation of flow. This phenomenon is noted whether testosterone propionate is administered intramuscularly, subcutaneously, or orally.[1] It has also been noted with pregnancy urine extracts and with progesterone.[14] It is because of this temporary increase that injections are given every two to four days instead of daily.

Second, the route of administration seems to play an important role in determining the total dosage required to control the bleeding. The subcutaneous route provides for a more prolonged and thus for a more effective per-dose action.[15] However, in actively bleeding cases, the first injection was given entirely intramuscularly for a rapid initial action, or else it was divided between the intramuscular and subcutaneous routes to sustain and prolong the initial reaction over a longer period of time. Case 1 revealed that under essentially similar conditions the dosage required by the subcutaneous route was one-half that required by the intramuscular route. This patient was on one occasion given 100 mg. of testosterone propionate in divided doses in the ten days before her period. Endometrial biopsy taken at the start of injections and on the fourth day of the succeeding period revealed endometrial hyperplasia both times. Even though a considerable reduction in flow had resulted, the endometrium had apparently not been affected at all. This finding, combined with the observation that three patients were found to be bleeding profusely from a different type of endometrium on separate occasions, serves to substantiate further the contention that it is to the myometrium, not the endometrium, that we must look for the factors controlling the amount and duration of uterine bleeding.

SUMMARY AND CONCLUSIONS

On the basis of certain physiologic properties of testosterone, a therapeutic rationale for its use in the treatment of metromenorrhagia was developed along physiodynamic lines. This has been founded in main on the action of testosterone on the myometrium, since the myometrial elements play such an essential role in the control of the amount of uterine bleeding.

The action of testosterone is, first of all, inhibition of rhythmic intermittent contractility, thus lessening the volume flow of blood *to* the uterus. Second, by its direct effect on the myometrial elements, the volume flow of blood *in* the myometrium is reduced. The net result is a diminution in the flow of blood to the endometrium with a consequent reduction in the amount of uterine bleeding.

The immediate treatment of metromenorrhagia with testosterone propionate proved to be highly successful.

The average minimal dosage required to lessen the bleeding materially varied from 10 to 30 mg. The total dosage necessary to stop the flow completely ranged from 10 to 120 mg., with an average of 40 to 60 mg. Two to four injections at intervals of two to four days were usually found sufficient. Injections should not be repeated during the transient exacerbation of bleeding which frequently occurs.

The subcutaneous route seems to provide for a more effective per-dose action, hence requires a smaller total dosage to achieve a therapeutic result. Where the flow was very profuse and free, the initial injection was given intramuscularly for a rapid initial action.

The only possible sign of defeminization ever observed was the loss of libido in two patients.

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REFERENCES

(1) *Abarbanel, A. R.:* Trans. Am. Assoc. Obst. Gyn. & Abd. Surg. (In press.) (2) *Klein, M., and Parkes, A. S.:* Proc. Roy. Soc. London **121:** 574, 1937. (3) *Hartman, C. G.:* Personal communications. (4) *Abarbanel, A. R.:* Unpublished data. (5) *Zuckerman, S.:* Lancet **2:** 676, 1937. (6) *Reynolds, S. R. M.:* Anat. Rec. **62:** 269, 1935. (7) *Leonard, S. L., Sager, V., and Hamilton, J. B.:* Proc. Soc. Exper. Biol. & Med. **37:** 362, 1937. (8) *Bartelmez, G. W.:* Contrib. to Embryol. (No. 142) **24:** 141, 1933. (9) *Daron, G. H.:* Am. J. Anat. **58:** 349, 1936. (10) *Fagin, J., and Reynolds, S. R. M.:* Am. J. Physiol. **117:** 86, 1936. (11) *Loeser, A. A.:* Lancet **1:** 373, 1938. *Geist, S. H., Salmon, U. J., and Gaines, J. A.:* Endocrinology **23:** 784, 1937. *Foss, G. L.:* Lancet **1:** 992, 1938. (12) *Beclere, C.:* Bull. Soc. Gynec. Obst. **27:** 747, 1938. (13) *Kenyon, A. T.:* Endocrinology **23:** 121, 1938. (14) *Jeffcoate, T. N. A.:* J. Obst. & Gynaec. Brit. Emp. **44:** 31, 1937. (15) *Deansly, R., and Parkes, A. S.:* Proc. Roy. Soc., London **124:** 279, 1938. (16) *Salmon, U. J.:* Proc. Soc. Exper. Biol. & Med. **38:** 352, 1938. (17) *Abarbanel, A. R.:* Am. J. Obst. & Gynec. **38:** 1043, 1939.

Osborn, G. R., and Dawson, J. C. C.: Air Embolism, Lancet **2:** 770, 1938.

Three instances of death following air embolism are reported, two in women following full-term delivery. In one case, death occurred three hours after cesarean section performed for a contracted pelvis and a large uterine fibroid. Temporary collapse followed incision of the uterine wall; but cyanosis persisted and obvious air hunger developed postoperatively. The second case followed natural delivery and apparently occurred following expression of blood clots from the uterus one-half hour post partum. Death ensued in one and one-half hours. Autopsy revealed a partial inversion of the uterus.

The characteristic symptoms of air embolism are described as sudden onset; disappearance of the pulse; deep respirations with air hunger; restlessness with chest discomfort; pallor if the case is fatal in one to two minutes and cyanosis if death is delayed.

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INHIBITION OF LACTATION DURING THE PUERPERIUM BY TESTOSTERONE PROPIONATE

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EXPERIMENTAL inhibition of lactation in mice has been accomplished with crystalline estrone by de Jongh[1] and Robson.[2] Enzmann and Pincus[3] inhibited milk secretion in lactating mice, and de Jongh[4] produced the same results in normal and ovariectomized lactating mice. Selye, Collip and Thompson[5] observed the inhibitory effect on lactation in rats after injection of anterior pituitary-like and pig pituitary extract. Connon[6] confirmed these findings. Robson[7] demonstrated in mice, and Folley and Kon[8] in rats that testosterone propionate inhibited lactation, while androsterone and progesterone were ineffective. Anselmino and Hoffmann[9] showed that progesterone does not exert an inhibitory action on the secretion of milk.

R. Kurzrok and O'Connell demonstrated recently that it is possible to inhibit lactation in women during the puerperium by the administration of male sex hormone in the form of testosterone propionate.

We are reporting a series of 56 patients treated with testosterone propionate in an attempt to inhibit lactation post partum. In order to determine the optimum dosage, the amount of sex hormone was varied, and in order to determine the most advantageous time of administration the injections were given at different stages after delivery. Most of these patients had normal deliveries; some were delivered by forceps, either elective or indicated, and several by cesarean section. These patients had no treatment to inhibit lactation other than testosterone propionate. Saline cathartics were not given and fluids were not restricted. Six patients had adhesive strapping and constrictive sheet binders because of pain and engorgement in the breasts. Most of the patients who had already begun to lactate complained of pains in the breasts, engorgement, and not infrequently showed an elevation of temperature prior to treatment. Indications for the avoidance of suckling were: (1) Cracked nipples, (2) premature infants, (3) stillborn infants, (4) refusal of mother to nurse child, (5) constitutional disease in mother, such as cardiac disease, pyelitis, etc.

Injections were given intramuscularly into the gluteal region. The male sex hormone had no apparent effect upon the amount or continuance of the lochia, involution of the uterus taking place at the normal rate. There were no unpleasant after effects, nor were any local infections or reactions noted. There were no painful contractions of the uterus following the injections, nor was there any effect on afterpains in those patients, particularly multiparas, who did complain of the usual cramps. Results were equally as good in multiparous and primiparous women. Onset of the first menstrual period was not delayed in those patients observed postpartum, nor did the bleeding differ in any way from that usually seen.

We have divided our cases into the following groups:

Group 1.—Two patients were treated by administration of 100 mg. of testosterone propionate on the day of delivery, in divided doses of 25 to 50 mg. Lactation was completely inhibited.

Group 2.—In 29 patients treatment was begun three days after delivery, 125 mg. of male sex hormone being given, usually in doses of 50, 50 and 25 mg. at twelve-hour intervals. In several cases, 25 mg. was administered every four hours. Ten patients complained of some engorgement and pain in the breasts for twelve to thirty-six hours, and binders or adhesive strappings were used in 8 cases. Ice bags were applied in 2 cases. Lactation occurred in these patients, but lasted only three to six days, and was never considerable in amount. The remaining 19 patients had

excellent results, lactation either not occurring or being present to a diminished extent for a few days without pain and congestion of the breasts.

Group 3.—In 11 cases treatment was begun 4 to 5 days postpartum. Five patients had good results, one patient requiring an additional 25 mg., making a total dosage of 150 mg. One patient obtained no relief from 100 mg. given in 2 injections of 50 mg. each, the breasts being hard and painful for the next twenty-four hours; at this time, another 100 mg. was administered, with marked relief within twelve hours. Four patients given an individual injection of 100 mg. showed little or no benefit, even when an additional 25 mg. was given.

Group 4.—In 8 patients, treatment was started from 6 to 9 days after delivery. One failure occurred, this patient receiving an individual dose of 100 mg. The other 7 patients responded favorably within twenty-four hours after the last dose, 125 to 150 mg. being administered in divided doses. One patient developed an elevated temperature of 105° shortly after the first injection; however, this was due to a concomitant pyelitis.

An interesting problem occurred in a multipara who returned to the hospital two weeks post partum because of bleeding. A diagnosis of retained secundines was made. The temperature of the patient had varied between 100° and 104° F., and nursing had been continued until admission to the hospital. The breasts were engorged and tender; 100 mg. of testosterone propionate was given, followed by 20 mg. twelve hours later. Within thirty hours, lactation had almost entirely ceased, the breasts were soft and not painful.

Another patient, a multipara, was delivered spontaneously after a short labor. During a previous pregnancy she had developed a mastitis, which subsided after several days. Four weeks following the recent delivery of a child she developed a fissure of the left nipple. Nursing produced frank bleeding, and breast feeding was discontinued; an ice cap was applied to the breast as well as an adhesive binder for twenty-four hours; 100 mg. of testosterone propionate was administered followed by 50 mg. at twelve-hour intervals until 250 mg. had been given. Within forty-eight hours after the final dose, the breast no longer lactated. Unfortunately, softening and fluctuation took place, and a breast abscess had to be incised. At no time after treatment did lactation occur. Secretion had ceased almost entirely within twelve hours after the injections.

DISCUSSION

1. At the present time we are unable to determine exactly the optimum time to administer the testosterone propionate in order to obtain optimum results.

2. Good results were uniformly obtained when the dose ranged between 125 and 150 mg. This dosage was apparently higher than that found necessary by R. Kurzrok and O'Connell.

3. Lactation, engorgement, and pains in the breasts did not recur after treatment was stopped.

4. Apparently better results were obtained when the total amount of medication was given in divided doses of 25 to 50 mg.

5. Individual doses of 100 and 125 mg. were generally ineffective regardless of the time of administration.

6. Fifty-six patients, post partum, were treated with testosterone propionate to inhibit lactation. Forty-nine patients responded favorably to this therapy. There were 7 failures in this series.

Since it is definitely possible to inhibit lactation by the use of testosterone propionate either before or after actual lactation has set in, we believe the mode of action of the drug is by inhibition of the pituitary, as demonstrated experimentally in animals. The fact that lactation can be prevented before its onset is evidence that the inhibitory effect is not on the end organ, namely, the breast tissue, but indirect, through the pituitary.

We wish to thank Drs. Irwin Schwenk and Max Gilbert of the Schering Corporation for their very helpful cooperation and for the generous amounts of material which they supplied.

REFERENCES

(1) *De Jongh, S. E.:* Acta brev. Neerland. **3:** 52, 1933. (2) *Robson, J. M.:* Quart. J. Exper. Physiol. **24:** 337, 1935. (3) *Enzmann, E. V., and Pincus, G.:* Am. J. Physiol. **103:** 30, 1933. (4) *De Jongh, S. E.:* Acta brev. Neerland. **3:** 88, 1933. (5) *Selye, H., Collip, J. B., and Thompson, D. L.:* Endocrinology **18:** 237, 1934. (6) *Connon, F. E.:* Proc. Soc. Exper. Biol. & Med. **37:** 52, 1937. (7) *Robson, J. M.:* Ibid. **36:** 153, 1937. (8) *Folley, S. J., and Kon, S. K.:* Proc. Roy. Soc., London, s. B, **124:** 476, 1938. (9) *Anselmino, K. J., and Hoffmann, F.:* Zentralbl. f. Gynäk. **60:** 501, 1936. (10) *Kurzrok, R., and O'Connell, C. P.:* Endocrinology **23:** 476, 1938.

THE USE OF TESTOSTERONE PROPIONATE IN THE INHIBITION OF LACTATION DURING THE PUERPERIUM*

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THE clinical observations during the lactating period in the puerperal woman and the problem of the inhibition of milk secretion have stimulated this report. In striving for a simpler and newer method of treatment for this uncomfortable condition, the use of testosterone propionate (oreton)† was employed and its results in a series of 50 cases are herewith presented.

The ever-increasing research in endocrinology has been apparent in offering a solution to the close interrelationship between the mammary glands during pregnancy and the puerperium and other hormones. As is well known, the human breast is prepared for lactation by being under the influence of the hormones of the ovary. Estrin has been demonstrated to be one of the factors which controls the growth and activity of the mammary gland.[1] The breast develops under the influence of the follicular hormone, while the corpus luteum hormone is responsible for the construction of alveolar tissues.[2] The work of Corner in 1930[3] suggests that the function of the ovarian hormones is primarily dependent upon the anterior hypophysis. It has also been shown that a specific lactation hormone, termed prolactin by Riddle, is formed in the anterior lobe of the pituitary gland, which is assumed to be the stimulus for milk secretion and has no direct influence on the development of the mammary glands.

Many conditions are encountered in the puerperal woman and child, in which nursing is not advised in some instances, in others it is impossible. Among the latter may be mentioned cardiac conditions, toxemias of pregnancy, cesarean section, stillbirths, miscarriages and missed abortions, unwed mothers, monstrosities, cracked, eroded, and retracted nipples, mastitis, tuberculosis, diabetes and economic reasons.

It has been shown that estrogenic substances have a depressing action on the hypophysis and that the secretion of milk which depends upon the anterior pituitary hormone, prolactin, undergoes the same inhibition. This has led to the use of folliculin in large doses to bring about a reduction in the flow of milk. The results of this treatment have not been very encouraging. Ramos and Colombo,[4] Lindemann,[5] Hoffmann,[2] and Adrian[6] used injections of folliculin in doses ranging from 25,000 to 260,000 rat units daily with variable success. The results with estrogenic substances in the inhibition of milk secretion, although fair, caused considerable afterpains and increased the blood flow in those patients upon whom it was administered.

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*Read at a meeting of the Clinical Society of the Brooklyn Women's Hospital, March 16, 1939.

†Grateful acknowledgment is offered to Schering Corp., Bloomfield, N. J., for their generous supply of oreton for clinical use.

The inhibition of lactation in the human being with testosterone propionate was encouraged by R. Kurzrok. Kurzrok's theoretical explanation for the action of this preparation is that testosterone suddenly inhibits the action of prolactin, the activator of the mammary gland, at the time of lactation. Robson[7] found that injections of testosterone propionate in oil, 0.1 mg. daily for twenty days, would rapidly bring lactation to an end in mice.

Kurzrok and O'Connell[8] have used testosterone propionate for the inhibition of lactation in doses ranging from 50 to 150 mg. They found success in 19 out of their 21 cases.

At the Brooklyn Women's Hospital from Dec. 1, 1938 to the present time, 50 patients in early lactation during the puerperium were treated with testosterone propionate (oreton). Total doses varying from 25 mg. to 125 mg. were given in divided doses every twelve hours, intramuscularly. No other measures such as breast binders (the latter were used only for support in cases of pendulous breasts), restriction of fluids, ice bags, or magnesium sulphate were used.

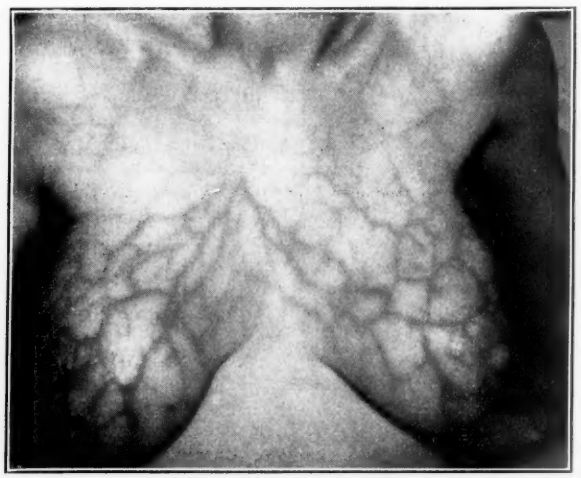

Fig. 1.—Infrared photograph. Note engorgement of breasts before treatment.

The ages of the 50 parturient women were between 20 and 38; 20 were primiparas, 30 multiparas. Thirty-two women delivered spontaneously, 12 with forceps, cesarean section 3, breech extraction 2, embryotomy 1. Reasons for delactation were as follows: Stillbirths 11, inverted nipples 9, section 3, sick infants 6, cracked and sore nipples 5, previous breast abscesses 2, cardiac 1, toxemia 4, bleeding nipples 1, unknown 8. Fourteen patients were treated with 75 mg. divided doses of 3 injections of oreton, 2 with 125 mg. in 5 divided doses, 33 with 30 mg. in 3 divided doses and one with 3 divided doses of 10 mg. each and subsequently one 50 mg. dose. Treatment was started on 4 patients on the second day post partum, 38 on the third day, 4 on the fourth day, 2 on the fifth day, 1 on the seventh day, and 1 on the twentieth day.

Forty-seven out of the 50 cases were definitely successful (94.0 per cent). In these cases, pain in the breasts due to congestion was the first symptom to disappear. On the average, this symptom disappeared eight to twelve hours after the total dose was administered. In all of the successful cases, cessation of lactation and complete involution of the breasts were present as early as the second day following total dosage.

The three unsuccessful cases were as follows:

CASE 1.—Mrs. B. W., aged 24 years, para i, gravida i, low forceps delivery, postpartum course negative, 125 mg. in 5 doses given, starting on the third day post

partum. Pain disappeared after twenty-four hours. Ninety-six hours after administration breasts only slightly improved, were caked and lumpy and there was no involution present.

CASE 2.—Mrs. P. G., aged 30 years, para ii, gravida ii, spontaneous delivery, post partum negative, inverted nipples, given 75 mg. in 3 doses, third day post partum. Ninety-six hours after administration no improvement, no involution, breasts were still full, hard, and congested.

CASE 3.—Mrs. L. L., aged 20 years, para i, gravida i, low forceps delivery, history of bleeding nipples daily in fourth and fifth months of pregnancy; salpingo-oophorectomy two weeks prior to delivery; given 80 mg. in 4 doses with no results; breasts were still full, congested and continually leaking.

A questionnaire was resorted to in an attempt to follow up the effect of the treatment. Thirty replies were received, the results being the following: (1) Milk did not return to the breasts in any of the 30 cases. (2) Twenty-seven women had no ill effects; 3 had slight pain in the breasts. (3) Twenty-four women menstruated promptly approximately six weeks following delivery. In 6 the menstrual flow had not as yet returned. (4) Out of 25 women, whose periods returned, the flow was more profuse than usual in 18, less than usual in 5, usual amount in 2. (5) None of the 30 women noticed any lumps in their breasts up to six weeks following delivery.

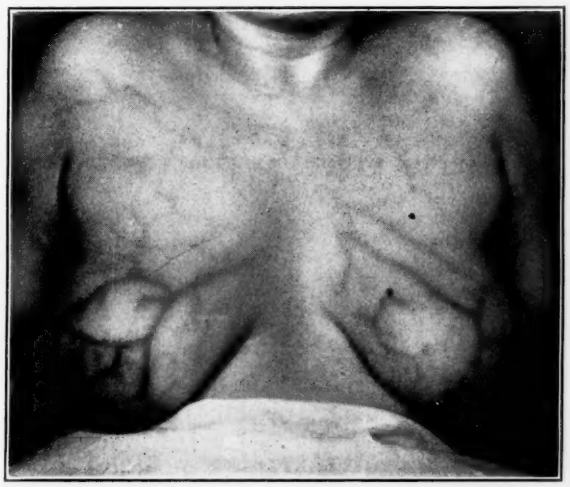

Fig. 2.—Infrared photograph. Note diminished engorgement of breasts after injection with testosterone propionate, 30 mg.

SUMMARY AND CONCLUSIONS

1. Fifty parturient women were treated with testosterone propionate (oreton) for inhibition of lactation. Two cases were observed as control patients. Successful cessation of lactation with alleviation of all symptoms was obtained in 47 or 94.0 per cent of the cases. The three unsuccessful cases are described.

2. The advantages of the use of testosterone propionate in inhibiting lactation in women during the puerperium are: Its simple administration, its good results, its alleviation of all symptoms in a great percentage of the cases, and the abandoning of other measures such as tight binders, ice bags, restriction of fluids, or magnesium sulphate with its use.

3. Afterpains were not exhibited after the injection of this hormone; likewise was there no evidence of excessive or diminished post-partum bleeding.

4. Smaller doses of testosterone propionate (three 10 mg. doses) can be used, and have been shown to be quite as effective as larger doses. This is encouraging, inasmuch as this form of treatment is within the economic means of the ordinary patient.

REFERENCES

(1) *Ballerby and Parkes:* J. Physiol. **62:** 301, 1927. (2) *Hoffmann:* Zentralbl. f. Gynäk. **60:** 2882, 1937. (3) *Corner:* Am. J. Physiol. **95:** 43, 1930. (4) *Ramos and Colombo:* Deutsche. med. Wchnschr. **64:** 782, 1938. (5) *Lindemann:* Zentralbl. f. Gynäk. **62:** 159, 1938. (6) *Adrian:* Bull. Soc. d'obst. et de gynéc. **27:** 331, 1938. (7) *Robson:* Proc. Soc. Exper. Biol. & Med. **36:** 153, 1937. (8) *Kurzrok and O'Connell:* Endocrinology **23:** 476, 1938.

706 EASTERN PARKWAY

ADENOACANTHOMA OF THE UTERUS

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CARCINOMA in general tends to reproduce, in a more or less disorderly fashion, the epithelium from which it arises. Therefore, cancer starting in the uterine cavity is usually composed of a cylindrical type of cell and tries to mimic the surface columnar epithelium and the glandular structures of the endometrium. These tumors are then frequently classified as adenoma malignum, adenocarcinoma, papillary adenocarcinoma, and alveolar or diffuse carcinoma. Occasionally, carcinoma of the body of the uterus is composed of cylindrical and squamous cells and in rare cases only squamous cells. Murphy,[1] in his report of 197 cases of fundal carcinoma admitted to the State Institute for the Study of Malignant Diseases at Buffalo, found but two cases of adenoacanthoma, while Lindsay[2] noted 3 instances in a series of 70 cases of carcinoma of the body of the uterus. Healy and Cutler[3] found 3 adenoacanthomas among 100 cases of carcinoma of the body of the uterus.

Adenoacanthoma, sometimes called adenosquamous carcinoma, is composed of groups of adenocarcinoma and areas of squamous epithelium. Usually the squamous epithelium is a benign accompaniment of the malignant cylindrical cell carcinoma, but it may sometimes undergo malignant change. Novak and Yui[4] believe that the squamous epithelium probably arises from undifferentiated cells beneath the cylindrical epithelium which under appropriate stimulation may develop into squamous epithelium. Occasionally the squamous cells may predominate, but most frequently it is the adenocarcinoma which forms the largest part of the neoplasm. In sections of these tumors one can frequently see how the squamous change occurs from the cylindrical cell thus indicating the primary character of the tumor. Sometimes, the squamous cells may be so few in number that they may be overlooked unless a careful search for them is made.

It is important to differentiate this type of tumor from the others because of its different behavior. Adenoacanthomas of the body of the uterus act similarly to adenocarcinoma of the body but their metastases are more frequent and extensive. The prognosis in these cases, according to Meigs,[5] lies midway between cancer of the cervix and cancer of the body. It responds quite poorly to radium. Healy and Cutler[3] reported three cases of adenoacanthoma which were treated with radium. Of these, one patient died in eleven months, one in 18 months, and the third in three years. According to Ferguson,[6] no reported case has been found where there was complete disappearance of the adenoacanthoma following the application of radium. Meigs[5] states that total hysterectomy, with the removal of both tubes, both ovaries and the cervix, is the proper treatment for this disease. Radium should be used as a palliative measure, as for example, in extensive cases when extirpation is impossible.

REPORT OF CASE

P. H., a white woman, 42 years of age, was admitted to the hospital Oct. 19, 1938, with the history of acute pain in the right side of the abdomen, accompanied by nausea and vomiting. For the past eight months she had similar attacks of pain in the lower abdomen associated with the above symptoms. Since this time she had anorexia and had lost some weight. Her bowel movements had been irregular. No bloody diarrhea was noted. For the past five months she had a purulent vaginal discharge. For three months previous to admission she had symptoms of urinary frequency and nocturia. The patient had never been pregnant. Her periods had always been irregular and usually lasted five days. For the last six months she suffered with menorrhagia and the last two months she developed metrorrhagia. Thirteen years before admission she bled considerably and was treated by curettage. This ameliorated her condition at that time.

Physical examination revealed a middle-aged woman who appeared very anemic. The pulse was 110, temperature 101.6° F., respiration 20, and the blood pressure 134/94. The skin was cold and clammy. The head revealed no abnormalities. The pupils reacted to light and accommodation. No neck glands were palpable. The breasts were normal. The heart was not enlarged and the sounds were of good quality. No murmurs were heard. The chest expanded equally on both sides and the breath sounds were clear. The abdomen was obese and there was slight generalized rigidity. Abdominal tenderness was generalized but was most marked in the right lower quadrant. Large masses were palpable in both lower quadrants. Vaginal examination revealed a soft, dilated cervix. A fungating mass was noted in the cervical canal. A biopsy taken from this mass revealed adenocarcinoma. The blood picture on Oct. 19, 1938, showed a hemoglobin of 100 per cent, red blood count 5,100,000, white blood count 10,900, polymorphonuclear neutrophiles 84 per cent, and lymphocytes 16 per cent. The sedimentation rate was twenty minutes. On Dec. 18, 1938, the red blood cells were 4,400,000 and the white blood cells 4,000. Urine examination on Oct. 19, 1938, was negative. On Oct. 22, 1938, examination showed many red blood cells and epithelial cells per high power field. On Oct. 24, 1938, phenolsulphonephthalein test was 22 per cent for two hours. On Oct. 19, 1939, the blood urea was 9.8 and the blood sugar was 105 mg. per 100 c.c. of blood. The blood Wassermann was negative. An electrocardiogram on Oct. 26, 1938, showed no evidence of myocardial disease.

The patient continued to vomit off and on. She was treated with infusions and transfusions. On Nov. 17, 1938, deep x-ray therapy was started. On Dec. 28, 1938, under cyclopropane anesthesia, a hysterectomy and a bilateral salpingo-oophorectomy were performed. The patient's condition was poor following the operation and a transfusion of 400 c.c. of citrated blood was given. On Dec. 31, 1938, she developed a decubitus ulcer. She was given 200 c.c. of citrated blood. Following the operation she was also treated with digalen and other stimulants. Her temperature was septic throughout her stay in the hospital, varying between 98.6° and 103° F. On Jan. 2, 1939, her temperature rose to 109° F., and she died shortly afterwards, five days following the operation.

Pathologic Report.—The specimen consisted of a uterus, two tubes, and two ovaries. The uterus was somewhat enlarged and measured 14 by 8 by 4.5 cm. Within the endometrial cavity, in the fundal portion, a large tumor mass was present. The tumor was papillary, friable, and reddish gray in color. It invaded the myometrium for a distance of approximately one-half centimeter. The endometrium immediately surrounding the tumor site was grayish white in color. The rest of the endometrial lining was thick, yellowish in color with areas of congestion. Both tubes were normal in length and showed no gross evidence of metastatic involvement. The right ovary was considerably enlarged and measured 10 cm. in diameter. Numerous cysts were present filled with a yellowish necrotic substance. Some of these cysts contained a papillary-like growth similar to that seen within the uterus.

Microscopic Findings.—The tumor of the uterus was composed of numerous acini some of which were small and others large. These were lined by single or multiple layers of cells which were columnar in type and hyperchromatic. Occasional mitotic figures were present. Some of the larger acini contained within them an amorphous, pink-staining substance within which fragments of nuclear material were present. Here and there groups of squamous cells were noted. In one area the surface of the uterine cavity was lined by a thick layer of large squamous cells (Fig. 1). In other areas of the tumor groups of squamous cells intimately associated with the tumor acini were present (Fig. 2). Here one could see how the columnar cells gradually merged into the squamous type of cell. Large areas of necrosis were present in which broken-down tumor cells were noted. The tubes showed some thickening of their villi but no tumor was noted within the lumen or involving the musculature. On the serosal surface, however, a few small groups of squamous cells were present. The right ovary was infiltrated with numerous tumor acini composed of hyperchromatic, columnar cells, showing occasional mitotic figures (Fig. 3). Large areas of necrosis were present. Areas of squamous cells were also noted. Some of these showed

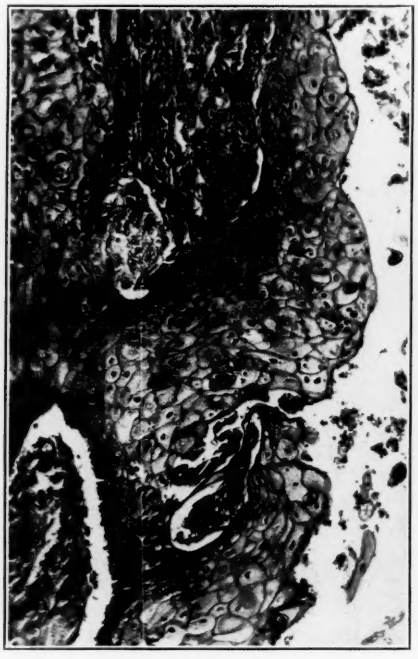

Fig. 1.

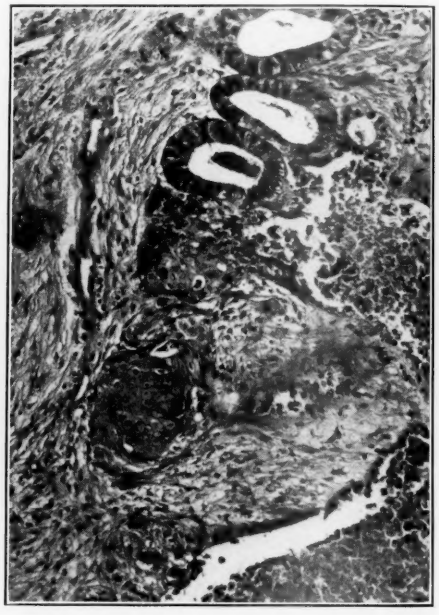

Fig. 2.

Fig. 1.—Section from epithelium lining the uterine cavity, showing thick well-differentiated squamous cells.

Fig. 2.—Tumor of uterus, showing cylindrical cell carcinoma in close association with the squamous cells.

keratinization and an occasional suggestive "pearl" could be seen. Groups of columnar and squamous cells were present and the intimate association between these two different types of cells could be observed (Fig. 4). The stroma of the tumor was composed of a loose type of connective tissue. The left ovary was normal.

Autopsy Findings.—The body was that of a well-developed and well-nourished, white female, about 40 years of age, with a body length of 166 cm. and a body weight of 160 pounds. No rigor mortis was present. There was a diffuse lividity in the dependent portions of the body. A decubitus ulcer was present in the sacral region which was not deep and measured 13 cm. in diameter. A linear surgical mid-

line incision, 21 cm. in length, extended from the umbilicus to the pubis. The edges of this incision were slightly inflamed. About 100 c.c. of a serohemorrhagic and purulent exudate was found within the peritoneal cavity. In the left lower quadrant of the abdomen, an abscess, measuring 6 cm. in diameter, was situated deep in the muscular wall. The mesenteric lymph nodes were slightly enlarged but showed no evidence of metastasis. The pleural and pericardial cavities revealed no abnormalities. The heart weighed 285 gm. and showed no gross pathologic changes. The right lung weighed 335 gm. and the left lung weighed 260 gm. There were extensive atelectatic areas in the posterior portions of both lower lobes. The bronchial tree was filled with mucus. The spleen weighed 250 gm. The pulp was light red in color, soft, and scraped easily. The splenic corpuscles were obliterated. The liver weighed 1,885 gm. The normal markings were not evident and it was soft in consistency. The biliary tract was normal. The pancreas weighed 130 gm. and showed no gross abnormalities. The left adrenal contained a small adenoma. The right adrenal was normal. The right kidney weighed 160 gm. and the left kidney weighed 165 gm. The capsules stripped with moderate resistance and the gross markings were slightly obscured. The gastrointestinal tract, ureters, and urinary bladder were normal. The uterus, tubes, and ovaries were absent due to operative procedure. No evidence of residual or metastatic neoplasms was found. A culture from the abscess of the abdominal wall revealed *B. coli* and *Staphylococcus aureus*.

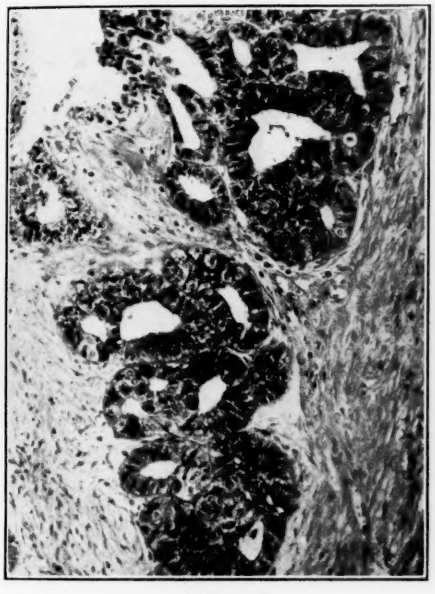

Fig. 3.

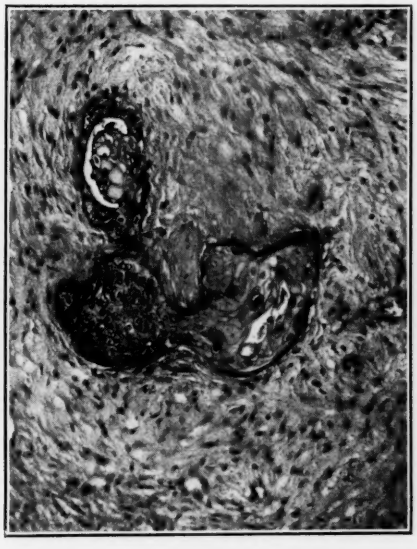

Fig. 4.

Fig. 3.—Metastatic tumor in ovary of typical cylindrical cell type.

Fig. 4.—The metaplastic change of squamous epithelium from the cylindrical epithelium is indicated in this section.

DISCUSSION

Since squamous cell carcinoma cannot arise directly from cylindrical epithelium, this latter type of tissue must undergo a transformation into pavement epithelium. This "epidermization" of the endometrial epithelium, according to Novak,[7] may be seen infrequently in benign lesions. This change may occur in either the surface epithelium or in the glands and is more common in the latter. Meyer[8] states that most frequently the squamous cell groups will project into the lumen of the gland in a glomerulus-like manner. It is also likely that when the endometrium projects into the muscular wall, the metaplastic changes may produce a picture which appears

to be that of malignant invasion. Various stands have been taken in the explanation of the "epidermization" of the endometrium. In 1885, Zeller[9] reported 63 cases of chronic "endometritis" in which he found the single layer of cylindrical epithelium had been replaced by many layers of squamous epithelium. These changes appeared to be due in most cases to long-continued intrauterine applications of iodine, bichloride of mercury or carbolic acid. Gebhard[10] and Flaischlen[11] reported cases where, in long-continued pyometra, the uterine cavity was frequently lined by squamous epithelium. Ries,[12] in 1896, reported a case of chronic inversion of the uterus, in which due to the exposure, dehydration and irritation, the mucosa was lined by squamous epithelium. Senile involution of the endometrium may be a factor in the causation of metaplasia but is an uncommon cause.

Besides these acquired factors, there is also the possibility of an embryonic cause. The highly differentiated epithelial cells found in the various parts of the genital tract are formed from a common type of cell in the Müllerian duct. Thus we have cylindrical, ciliated epithelium in the tubes, the cuboidal, ciliated cell in the corpus, the columnar mucus-producing cell of the cervical canal and the squamous cell type of the pars vagina. Sometimes this squamous variety extends into the cervical canal. Gellhorn[13] suggests that "aberrant" squamous cells may be left in the uterine mucosa or that some undifferentiated cells remain in the uterus and later develop into squamous cells. Natanson[14] found squamous cells in the uteri of the newborn and in infants up to two years of age. Hintze,[15] R. Meyer,[16] Polano,[17] and Sitzenfrey[18] found squamous cell groups in the hyperplastic endometrium and in true adenoma. The possibility that these misplaced cell groups may undergo malignant change is quite conceivable. Goldschmidt[19] and Lissowetsky[20] believe that these tumors develop from heterotopic collections of germinal or Müllerian epithelium. Engelhard[21] does not believe that metaplasia is sufficient to explain the variations in the cellular configurations of endometrial carcinomas. He also favors the embryonic origin. Novak,[7] however, states that he has never observed collections of such cells in the adult uterus and feels that these are lost as a result of the desquamation due to menstruation and pregnancy. He, therefore, concludes that the "epidermization" represents a genuine metaplasia of the cylindrical to the squamous type of epithelium.

Metaplastic changes is not at all uncommon in other parts of the body. Epidermoid carcinoma has been found in the lung, gall bladder, thyroid gland, pancreas, stomach, intestine, and breast. The epithelial cells in embryonal life have the potentialities of forming different types of epithelium, and it is in the basal cells that this potentiality is not lost.

This squamous metaplasia is seen most frequently in adenoacanthoma of the uterus. Gellhorn[13] notes that there have been approximately 25 cases of primary squamous cell carcinomas reported in the literature. There are then the various combinations of squamous and cylindrical cell tumors which are more frequent than the above but are not common. Epithelial pearl formation has been found in this type of neoplasm. Considerable discussion has occurred as to whether this tumor has a double origin or whether it is a squamous transformation in an adenocarcinoma. The latter viewpoint is the one most favorably received at the present time.

SUMMARY

Adenoacanthoma is an uncommon tumor of the uterus. This tumor apparently arises as a metaplastic change in the cylindrical cells of an adenocarcinoma of the body of the uterus.

The prognosis in these cases is poor and appears to lie midway between that of a carcinoma of the body of the uterus and a carcinoma of the cervix.

REFERENCES

(1) *Murphy, W. T.:* Radiology **26:** 178, 1936. (2) *Lindsay, W. S.:* Surg. Gynec. Obst. **44:** 646, 1927. (3) *Healy, W. P., and Cutler, M.:* Am. J. Obst. & Gynec. **19:** 457, 1930. (4) *Novak, E., and Yui, E.:* Ibid. **32:** 674, 1936. (5) *Meigs,*

J. V.: Tumors of the Female Pelvic Organs, New York, 1934, The Macmillan Co., p. 140. (6) *Ferguson, J. A.:* New England J. Med. **204:** 1359, 1931. (7) *Novak, E.:* Am. J. Obst. & Gynec. **18:** 449, 1929. (8) *Meyer, R.:* Ztschr. f. Geburtsh. u. Gynäk. **85:** 441, 1923. (9) *Zeller, A.:* Ibid. **11:** 56, 1885. (10) *Gebhard, C.:* Ibid. **24:** 1, 1892. (11) *Flaischlen, N.:* Ibid. **32:** 347, 1895. (12) *Ries, E.:* Am. Gynec. & Obst. J. **8:** 184, 1896. (13) *Gellhorn, G.:* Am. J. Obst. & Gynec. **31:** 372, 1936. (14) *Natanson, K.:* Monatschr. f. Geburtsh. u. Gynäk. **26:** 350, 1907. (15) *Hintze, O.:* Zentralbl. f. Gynäk. **52:** 2209, 1928. (16) *Meyer, R.:* Arch. f. Gynäk. **115:** 394, 1922. (17) *Polano, O.:* Ztschr. f. Geburtsh. u. Gynäk. **67:** 411, 1910. (18) *Sitzenfrey, A.:* Ibid. **59:** 385, 1907. (19) *Goldschmidt, A.:* Ibid. **113:** 306, 1936. (20) *Lissowetsky, V.:* Act. Cancerol. **2:** 27, 1936. (21) *Engelhard, J. L. B.:* Nederl. Tijdschr. v. verlosk. en gynaec. **38:** 163, 1935.

CLINICAL EXPERIENCES WITH STILBESTROL (DIETHYLSTILBESTROL)

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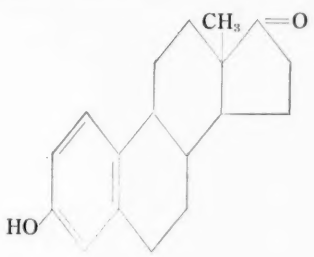
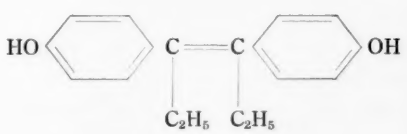
In 1938 Dodds[1] and his associates introduced a new synthetic preparation with effective estrogenic properties, 4-4′ dihydroxy a.b. diethyl stilbene for which the name diethyl stilbestrol was proposed and later abbreviated to stilbestrol. Reports in the foreign literature, particularly the British,[2-5] seem to indicate that this substance possesses estrogenic activity comparable if not superior to the biologic estrogens in vogue in the United States.

Because of its availability with as many as 125,000 international units per c.c., its previous clinical acceptability abroad and its relative economy, we were led to utilize this drug* in a series of cases in which estrogenic therapy was indicated.

Stilbestrol can be easily synthesized and does not contain the phenanthrene nucleus formerly thought to be an essential component of an estrogenically active substance.



Estrone



Diethylstilbestrol

*We wish to express our appreciation to the Winthrop Chemical Company for supplying us with the diethylstilbestrol used in these cases.

The product used in this study was standardized by the Allen-Doisy method, and when standardized in this manner, 1 mg. of stilbestrol was found to have the same activity as 25,000 I.U. of estrone.[6, 9] Dodds, Lawson, and Noble[6] found diethylstilbestrol to be approximately two and one-half times as potent as estrone in producing vaginal estrus in ovariectomized rats, and that the compound definitely stimulated uterine growth. The latter property has also been observed in the human being.[2, 4]

Stilbestrol possesses other properties characteristic of natural estrogens as evidenced by its power to suppress the production of the anterior pituitary gonadotropic and growth hormones,[7] its capacity to suppress the action of progestin,[8] its adverse effects upon lactation,[5, 8] and its ability to sensitize the uterus of immature rabbits to progesterone.[6] The effect of this synthetic estrogen on breast tissue is similar to that of estrone but much less marked.[6]

Studies in toxicity[9] "indicate a broad margin of safety between the toxic and the effective dose for the laboratory animal. The intravenous lethal dose for the cat (the lowest for any animal tested) is 30 mg./Kg."

MATERIAL

Our clinical material consists of 50 cases from the Hutchinson Memorial Clinic of Tulane University of Louisiana, and the private practice of one of us (C. G. C.). In this group of 50 patients, there were 19 classed as having a physiologic menopausal syndrome (Group I). Sixteen patients had postoperative or postradiation menopausal syndromes (Group II), while 13 cases were classified as manifesting hypoestrinism (Group III). In addition there were two cases of senile vaginitis.

GROUP I. PHYSIOLOGIC MENOPAUSAL SYNDROME

The physiologic menopausal syndrome group contained 19 patients ranging in age from 30 to 55. Their complaints included various combinations of the following symptoms: Headache, dizziness, nervousness, hot flushes, depression, muscle and joint pain, frigidity, insomnia, vaginitis and irritability. One patient in this group had diabetes insipidus as a complicating factor.

The same method of individualized treatment outlined for the previous group was followed. However, it was found necessary to employ larger dosage in some of the younger members of this group to maintain a satisfactory control of symptoms.

The therapy in this group was individualized in accord with the severity of the presenting symptoms. Early in the series we gave injections of 1 mg. (25,000 International Units) once or twice weekly, but later it was found more efficacious to start with a large initial dose of 5 mg. (125,000 I.U.), decreasing the amount administered as the symptoms were controlled. More recently, we have substituted oral administration when the symptoms were adequately alleviated by intramuscular therapy. It was found that successful oral administration required approximately three times the quantity previously given by the intramuscular route.

GROUP II. SURGICAL MENOPAUSAL SYNDROME

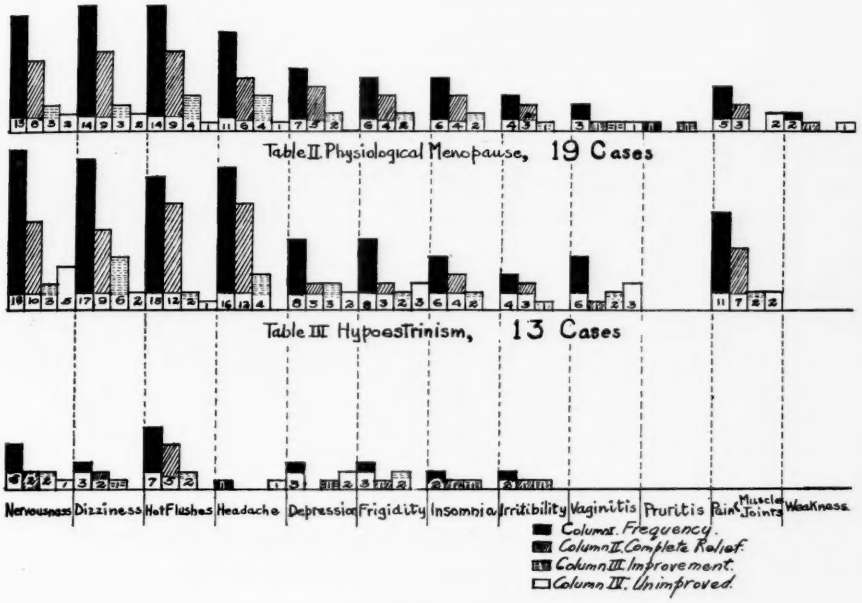
There were 16 patients ranging in age from 20 to 60 years in this group. The interval between operation or irradiation and the inauguration of stilbestrol therapy varied from three months to twenty-five years. Likewise the symptoms varied in number and intensity, and included the following: nervousness, dizziness, flushes, headache, depression, muscle and joint pain, frigidity, insomnia, vaginitis, pruritus, weakness, and irritability. One patient in this group had diabetes insipidus as a complicating factor.

GROUP III. HYPOESTRINISM

There were 13 patients in this group, ranging in age from 21 to 36 years, and manifesting symptoms attributable to estrogenic insufficiency. The complaints presented by these patients included nervousness, dizziness, flushes, headache, depression, frigidity, insomnia, and irritability, especially marked at the menstrual period. In addition, two patients complained of dysmenorrhea, one of hypomenorrhea, and one patient had peripheral edema associated with the menstrual period. The patients with dysmenorrhea were markedly improved and the patient with menstrual edema obtained prompt relief. The effectiveness of stilbestrol therapy in the remaining members of this group is indicated in Table III.

Again the therapeutic regime employed was similar to that previously discussed, in that each case was individualized and the dosage varied according to the severity of the symptoms. Here, however, the drug was administered according to that time of the menstrual cycle at which the symptoms appeared. In general, smaller dosages sufficed to eradicate adequately and to alleviate symptoms. Usually 5 mg. were given intramuscularly approximately two days before the periodic onset of symptoms.

TABLE I. SURGICAL MENOPAUSE, 16 CASES



SENILE VAGINITIS

In our series there were 2 cases in which senile vaginitis was the only complaint. These were promptly relieved by stilbestrol given intramuscularly in dosage of 5 mg. once weekly. The patients' reports of symptomatic improvement were concurrent with the finding of increased cornification as evidenced by vaginal smears.

RESULTS

Tables I, II, and III summarize in detail the results obtained in the three larger groups of patients treated with stilbestrol. One can observe at a glance that the more frequent and disturbing symptoms, such as headache, nervousness, dizziness, and hot flushes, are successfully relieved in a large and gratifying percentage of cases. We were pleased to observe that patients frequently reported relief of symptoms very shortly after the inauguration of therapy. The improvement that stilbestrol yields

in muscle and joint pain and frigidity is not as impressive as the effectiveness of this synthetic estrogen on the other symptoms, but is as good as we have previously obtained with biologic estrogens.

It is interesting to note that 16 of these patients had previously received estrogenic therapy with biologic preparations, the total dosage ranging from 12,000 to 125,000 I.U. Of these, 13 were relieved of their symptoms and were maintained satisfactorily when stilbestrol was substituted. Three patients of this group obtained no relief from their previous therapy, and of these, 2 were completely relieved by stilbestrol, the third showing only slight improvement.

TOXIC EFFECTS

In this series no patient completely intolerant to stilbestrol was encountered. Approximately 60 per cent of the patients complained of nausea at some time during the treatment, an observation also made by others.[3-5, 10] The nausea was usually mild and transitory in nature, and was successfully relieved by decreasing the dosage, and very frequently did not recur despite the continued use of the same quantity which previously invoked nausea. When nausea followed oral administration, it was frequently lessened or relieved by changing to intramuscular injection. It has been our experience that patients are more tolerant to intramuscular than to oral administration of the drug.

In only one case was the nausea sufficiently severe to cause cessation of therapy for the period of a week, following which therapy was resumed without untoward effect. In one case a dermatitis appeared which may possibly be attributable to stilbestrol. In a new series of patients to whom the stilbestrol is to be administered solely per os, sodium bicarbonate will be given in 4 gm. doses simultaneously. Our experience indicates that the concurrent use of sodium bicarbonate with stilbestrol seems to lessen nausea.

RECOMMENDATIONS

Our observations regarding the administration of stilbestrol where estrogenic therapy is indicated lead us to suggest that: (a) therapy be individualized; (b) the initial administration be by the intramuscular route and preferably in large doses (5 mg. once or twice weekly); (c) when symptoms are controlled the dosage may be reduced to 1 mg. once or twice weekly; (d) a patient adequately maintained on such dosage may have oral administration substituted for intramuscular; (e) the dosage for oral therapy should be successful if given in a quantity equivalent to three times the previous intramuscular administration; (f) when oral administration is utilized sodium bicarbonate should be administered concomitantly.

CONCLUSIONS

1. The pharmacology, physiology, and toxicity of a new synthetic estrogen, "stilbestrol," containing 25,000 I.U./mg. is discussed.

2. Our experience in 19 cases of physiologic menopausal syndrome, 16 cases of surgical menopausal syndrome, 13 cases of hypoestrinism and 2 cases of senile vaginitis is presented.

3. The results indicate that these types of cases may be satisfactorily controlled with this new synthetic estrogen as efficiently as with the available biologic estrogenic substances and stilbestrol is recommended because of ease of administration, relative low cost, and the wide range of utility.

4. Oral administration of stilbestrol has yielded satisfactory results in those patients to whom it has been given. We are presently extending our observations on this mode of administration.

REFERENCES

(1) *Dodds, E. C., Goldberg, L., Lawson, W., and Robinson, R.:* Nature **141:** 247, 1938. (2) *Englehart, E.:* Wien. klin. Wchnschr. **51:** 1356, 1938. (3) *Bishop, P. M. F., Boycott, M., and Zuckerman, S.:* Lancet **1:** 5, 1939. (4) *Winterton, W. R., and MacGregor, T. N.:* Brit. M. J. **1:** 7, 1939. (5) *Kellar, R. J., and Sutherland, J. K.:* J. Obst. & Gynaec. Brit. Emp. **46:** 1, 1939. (6) *Dodds, E. C., Lawson, W., and Noble, R. L.:* Lancet **1:** 1389, 1938. (7) *Noble, R. L.:* Lancet **2:** 192, 1938. (8) *Parkes, A. S., Dodds, E. C., and Noble, R. L.:* Brit. M. J. **2:** 557, 1938. (9) Winthrop Chemical Co.: Communication. (10) *Loeser, A. A.:* Brit. M. J. **1:** 13, 1939.

HYALINE ADENOMA OF THE CERVIX

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SEVERAL months ago a specimen of cervical tissue was examined which presented a puzzling and unique histologic pattern. According to the history, a diagnosis of adenocarcinoma of the cervix had been made two years before, and a supracervical hysterectomy performed. Upon examination of the uterus after its removal, no tumor could be found, but a deep longitudinal groove was noted in the lower segment, which was regarded as the probable source of the material obtained for biopsy, and it was assumed that the tumor had been completely removed by the curette. During the interval of two years nothing unusual had been observed in the cervical stump, until the development of a soft, diffuse, polypoid formation, extending about an inch up into the cervical canal, had prompted the removal of the specimen just mentioned for further examination. The specimen was compared with that examined two years before, and the patterns of the two were found to be essentially alike.

Since the biology of this tumor and the unusual histologic pattern made it inadvisable to diagnose the tissue as malignant, the descriptive term "hyaline adenoma" was adopted. A search of the files back to 1928 disclosed two other tumors of a similar character, but lacking the hyaline stroma, both of which had been classified as adenocarcinoma of the uterus. The clinical records of, and meticulous histologic study of, the tissue removed from the three patients clearly show that these tumors are not cancer.

The first patient was a 27-year-old woman, married for two years, obese, always regular in her menses, and who had had a cervical discharge for ten years. When she finally consulted a regular physician after years of osteopathic treatment for back pain, a polypoid formation extending high in the cervical canal prompted the biopsy, which resulted in the diagnosis of adenocarcinoma and the supracervical hysterectomy just described. Fig. 1 shows the pattern of the cervical tumor found in the initial biopsy. The hysterectomy without removal of the cervix afforded an excellent opportunity to study the biology and subsequent progress of this tumor. Two years later, as described in the first paragraph, the second biopsy was made; six months later, the third, which is shown in Fig. 2, and after another interval of ten months, a fourth biopsy. No evidence of malignancy ever developed from a clinical point of view. The second biopsy specimen is not presented because of poor contrast for microphotographic work, but in it the glandular elements had almost disappeared, and between the hyaline islands vascular granulation tissue and pale hydropic squamous epithelial cells, showing both intracytoplasmic and intranuclear edema, were the essential features. It is to be noted that in the third biopsy the epithelial islands were quite healthy and distinct. The latest biopsy has shown no significant change during the past ten months, and the squamous epithelium is less prominent.

The second patient, a 40-year-old woman, obese, married three years, and never pregnant, was also subject to back pain. Her periods had always been profuse,

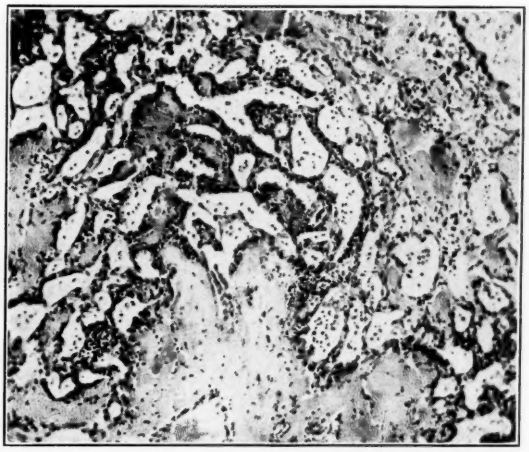

Fig. 1.—Initial biopsy. A conglomeration of cervical glands, showing variable degrees of hyperplasia, squamous metaplasia, secretory activity and disorganization, are supported by a stroma consisting almost entirely of hyalinized connective tissue. About 50 per cent of the tissue is hyaline, which stains characteristically by the Van Gieson technique. Mucus and neutrophiles occupy the gland lumens.

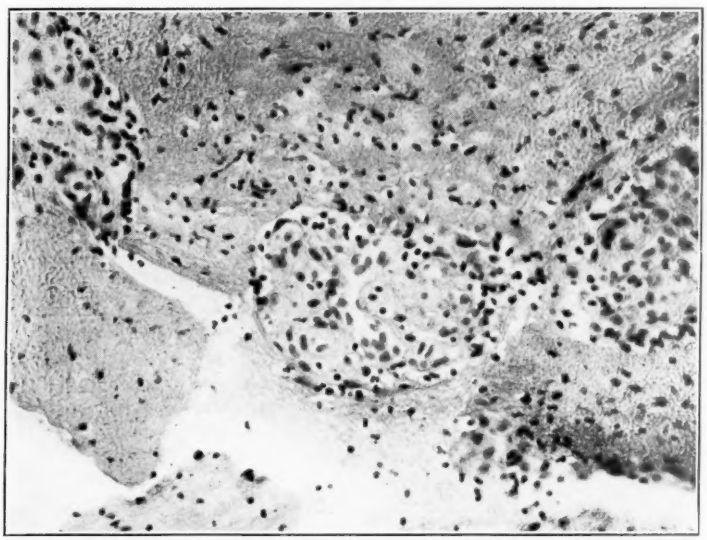

Fig. 2.—Hyaline adenoma of cervix (hematoxylin and eosin). Third biopsy. (Two and one-half years after initial biopsy. Magnification twice that of Fig. 1.) Recurrence of the original cervical tumor. No glandular elements could be found. Small islands of somewhat hyperplastic squamous epithelium are imbedded in hyalinized connective tissue, and are derived from glandular epithelium which has undergone squamous metaplasia. This recurrence occurred one inch above the external os in the cervical canal.

A biopsy six months before this had shown a marked increase in the hyaline stroma, disintegration of glandular structures, areas of vascular granulation tissue surrounded by hyaline, and surface sloughing. Squamous epithelium at that time was scant and hydropic, showing both intracytoplasmic and intranuclear edema.

The most recent biopsy, ten months after the third, has shown little change other than further increase in the hyaline reaction with less squamous epithelium.

and for the preceding three years irregular and lasting from sixteen to twenty days. Both her mother and sister had menstruated regularly throughout their pregnancies. Three years ago the cervix and uterus were curetted, and a laparotomy performed, although only the appendix and an ovary were removed, because the uterus appeared normal. The curettings were reported as adenocarcinoma of the cervix (Fig. 3) by two pathologists, and irradiation was administered to the uterus and cervix. Another biopsy, made just before irradiation treatment was begun, showed only a low grade, chronic inflammatory reaction with no evidence of remnants of the original tumor. Management was based upon the tissue obtained in the original curettage. No further abnormalities developed, and for the past three years she has been regarded as cured.

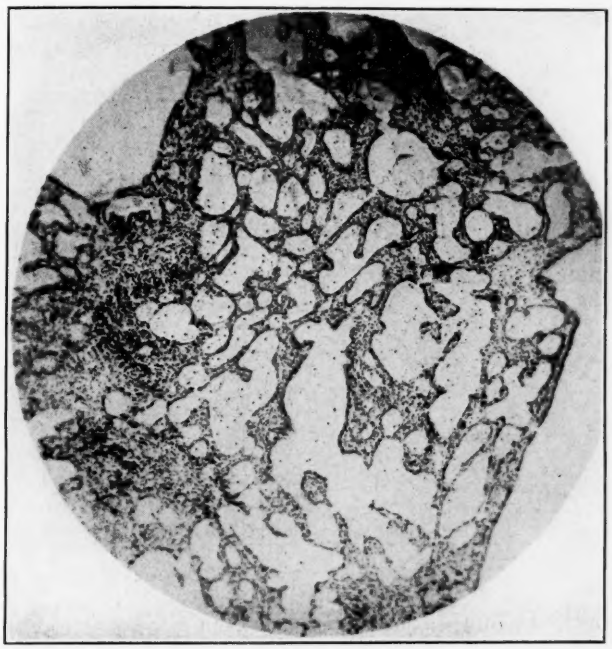

Fig. 3.—Adenoma of cervix without hyaline stroma. (Hematoxylin and eosin.) The glandular pattern of this tumor so closely resembles that of the hyaline adenoma, shown in Figs. 1 and 2, that it seems allied to it. Here the stroma is scant, but without any hyalinization. Gland septa have broken down, and the confluence of the glands has produced a diminutive cystadenomatous formation. Many glands are cystic, and neutrophiles are present in their lumens. Endometrium present in the curettings showed the pathologic follicular phase, with cystic and dilated glands. Mucicarmine stains demonstrated an abundance of mucus in the cells and lumens of the cervical glands.

The third patient, a 42-year-old woman, underwent a panhysterectomy for fibroids, but died forty-eight hours after the operation. Besides multiple intramural leiomyomas, the uterus presented rough, granular, shaggy tabs involving the mucosa of the lower segment and cervical canal, which on histologic examination invited the diagnosis of low grade adenocarcinoma (Fig. 4). Menorrhagia and metrorrhagia had developed five months before operation, with back pain and low abdominal cramps, prior to which she had experienced no abnormalities. Early menopausal symptoms were also noted. She had been married since the age of 17, and one abortion eighteen years before admission constituted the only pregnancy.

Because of the unusual interest of the first of these three lesions, and since all three types are undoubtedly being encountered from time to time, it is felt that the presentation of these three cases will be of interest. I can find in the literature no reference to the pathologic entity which I have described as a hyaline adenoma, but the other two are occasionally mentioned as adenomatoid hyperplasias of the

cervical glands,[1] and Oppenheimer,[2] in 1932, reported a diffuse polypoid hypertrophy of the cervical mucosa in the nulliparous cervix.

Since the first patient with the hyaline adenoma had had a cervical discharge for ten years, and since the glandular patterns of the lesions of the others are very similar, but lacking the hyaline stroma, it is possible that their shorter duration without prolonged inflammatory irritation may explain the absence of the hyaline. Neither of these two lent themselves to the follow-up study possible wi[t] the first.

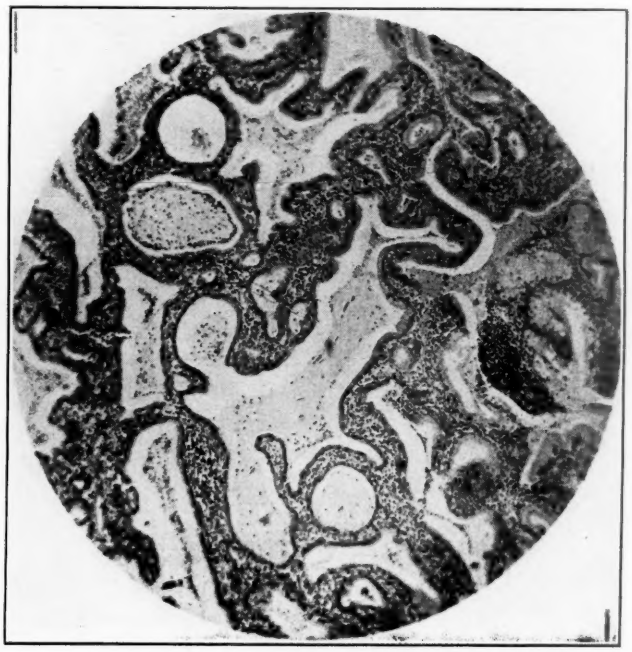

Fig. 4.—Adenomatoid hyperplasia of cervical glands. (Hematoxylin and eosin.) This specimen perhaps represents the youngest form of the process terminating in hyaline adenoma, and is typical of an inflammatory reaction in glandular polypoid tissue, with marked multiplication of the glands and a tendency to squamous metaplasia, warranting its inclusion in this series. Neutrophile infiltration is marked in the stroma and gland lumens. Hyalinization is not present. Endometrium accompanying the cervical curettings showed the early follicular phase.

SUMMARY

A tumor of the cervix, termed hyaline adenoma, the evolution of which has been observed in situ for over three years, is described. Two other lesions simulating it, but lacking the hyaline stroma, are also presented. The study of the life cycle of the hyaline adenoma has shown that its first stage consists of a proliferation of small, dilated and cystic cervical glands enclosed in a dense hyaline stroma which comprises about 50 per cent of the microscopic fields, and in which the glandular epithelium is disorganized and shows considerable squamous metaplasia. Subsequent biopsies exhibit disintegration and disappearance of the glands and the development of small islands of squamous epithelium with further proliferation of the hyaline stroma in which they are imbedded, but manifesting no evidence of malignancy.

The two lesions presented as similar to the hyaline adenoma and tentatively regarded as its possible precursors, would be more properly classified as adenomatoid glandular hyperplasia. These entities are believed to be of inflammatory origin, thus far reported only in the cervix of nulliparous women.

REFERENCES

(1) *Laffont, A., Montpellier, J., and Laffargue, P.:* Gynéc. et obst. **32:** 390, 1935. (2) *Oppenheimer, W.:* Arch. f. Gynäk. **150:** 741, 1932.

TUBAL PREGNANCY ASSOCIATED WITH TUBERCULOUS SALPINGITIS

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TUBAL pregnancy associated with tuberculous salpingitis is a very rare occurrence. Recently Stevenson and Wharton reported such a case, believed to be the first reported from the English-speaking world.* They have reviewed the literature and found only eight proved cases. For a summary of these cases the reader is referred to their article.

We desire to record another case of coincidental tubal pregnancy and tuberculous salpingitis, apparently the first to be reported from Canada and the third from the English-speaking world.

Mrs. K. H., white, aged 32 years, married five years, no previous pregnancies, was admitted to Victoria Hospital Feb. 17, 1939, and was discharged on March 7, 1939.

Past History.—The patient was born in England and came to Canada at the age of six years. She has had no serious or significant illnesses, no operations and in general has enjoyed reasonably good health. She was never suspected of having tuberculosis. Five years ago she was told that she had a gastric ulcer but this diagnosis was never proved, and she is now free from gastric symptoms. For two years she has frequently suffered from crampy lower abdominal pains, midline and in both lower quadrants, more severe a week before and just after her menstrual periods. Her menstrual cycle has been regular every twenty-eight to thirty days, moderate flow lasting three to four days with severe pain during the first day, no intermenstrual bleeding, no periods of amenorrhea prior to the present pregnancy.

Present Illness.—The patient's last normal menstrual period was on Dec. 25, 1938 but between that date and Jan. 25, 1939 she had a small amount of spotty vaginal bleeding. After January 25 the spotting stopped and some morning sickness and vomiting commenced. Her breasts became quite sore and enlarged. She believed that she was pregnant. All during this time the lower abdominal pain, which she had experienced for two years, was still present. About Jan. 25, 1939 she consulted her doctor for this longstanding abdominal pain. Pelvic examination was difficult and quite unsatisfactory, due to tenderness and a small introitus. Between Feb. 3, 1939 and Feb. 17, 1939 the patient had three attacks of severe lower abdominal and pelvic pain, lasting two to three hours. During the first attack she vomited but no vomiting took place in the two subsequent ones. The pelvic organs were tender and painful. After the second attack she felt very weak but did not faint. On the day of admission (Feb. 17, 1939) the third attack of severe abdominal pain began at 6 P.M. The pain was crampy, situated about 1½ inches below the umbilicus and lasted two to three hours. She was brought to the hospital by ambulance at 11 P.M. All during this time after Jan. 25, 1939 there was no vaginal bleeding. On admission her temperature was 100° F., pulse 80, hemoglobin 75 per cent, white blood cell count 13,650. Pelvic examination revealed a slightly enlarged uterus with a softened cervix. No blood was present on the examining fingers. The abdomen was tender throughout but not rigid and no masses could be detected. Operation was performed at 3 A.M. on Feb. 18, 1939.

*Since this paper was submitted, our attention has been called to the report of another case by Dr. Arthur Stein of Chicago (see reference).

At operation the abdomen was full of blood, part of which was fresh and unclotted, while many dark clots were also present. The uterus appeared slightly enlarged. The pelvic peritoneum and pelvic viscera were congested. Numerous fibrous pelvic adhesions were present. The right tube was thickened but its ostium was patent. The distal portion of the left tube was embedded in a mass of blood clot. This portion of the tube was grossly enlarged and had ruptured. Blood was oozing from the rupture and grayish villous tissue was protruding through the break in the wall of the tube. The condition was obviously a ruptured tubal pregnancy. Both ovaries appeared essentially normal. The left tube was removed. The fetus itself was not observed. Tuberculous salpingitis was not suspected at the time of operation. For two days postoperatively the patient's temperature rose to 103° F. and her pulse rate to 120. Then gradually both returned to normal. Four days after operation she expelled a piece of tissue which on microscopic study proved to be a decidual

Fig. 1. Fig. 2.

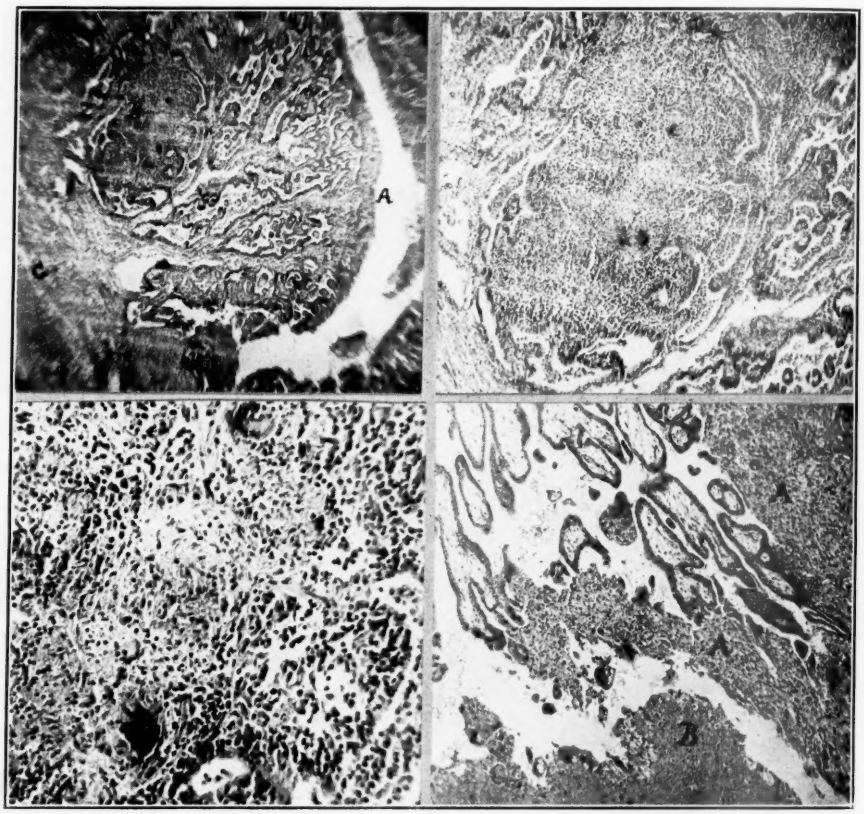

Fig. 3. Fig. 4.

Fig. 1.—Section across the tube proximal to the pregnancy. Note the matting together of the mucosal folds forming pseudoglandular spaces. *A* indicates the lumen; *B*, a tuberculous area; and *C*, the wall of the tube. (×36.)

Fig. 2.—An enlarged view of area *B*, showing conglomerate tubercles with two giant cells. (×72.)

Fig. 3.—High power view of tuberculous area *B*. Note the numerous lymphocytes and plasma cells and two giant cells. (×230.)

Fig. 4.—Section across the ampullary portion of the tube showing the pregnancy. Syncytial knots, masses of trophoblastic epithelium and numerous well-formed chorionic villi are shown. *A* indicates areas of trophoblastic epithelium (Langhans' cells). *B* is a mass of blood clot. (×72.)

cast. Otherwise her postoperative convalescence was uneventful and she was discharged from the hospital in good condition.

Pathologic Report.—The left tube measured 6 cm. in length. The narrow proximal segment measured 1.5 cm. in its greatest diameter. Its wall was somewhat thickened, its lumen slightly dilated and its mucosal folds were edematous. The ampullary segment was embedded in a mass of blood clot which, when gently lifted and partially dissected away, revealed a friable villous tissue and a small gestation sac which was ruptured and empty. The gestation products and blood clot were protruding through a gross rupture in the wall of the tube. The fimbriae were little distorted and the abdominal ostium of the tube was patent. Tuberculous salpingitis was not suspected until the microscopic sections were seen.

Microscopic sections through the isthmus and the ruptured ampullary portion were studied. The latter portion showed masses of fresh and older blood clot, numerous well-formed and well-preserved chorionic villi and syncytial masses (Fig. 4). The mucosa of the tube was destroyed at this level. The wall of the tube was much thinned out, moderately edematous and infiltrated with lymphocytes. The trophoblastic epithelium was active and had infiltrated deeply into the wall of the tube where there was also a moderate decidual reaction. In the section through the isthmus most of the plicae were fused together forming pseudoglandular spaces containing blood and desquamated epithelial cells (Figs. 1 and 2). The stroma of the plicae, the submucosa, and wall of the tube were heavily infiltrated with lymphocytes (Figs. 2 and 3). The wall of the tube was not thickened. Its muscularis seemed to be deficient. Numerous discrete and conglomerate tubercles were situated in the plicae, submucosa and in the subserous tissue of the tube. Some of these possessed central giant cells and the larger tubercles showed caseous centers (Fig. 3). Vascular fibrous adhesions were attached to the serous surface of the tube. The pathologic diagnosis was: ruptured tubal pregnancy (left) associated with tuberculous salpingitis.

COMMENT

It is probable that this patient suffered from tuberculous salpingitis and pelvic peritonitis for quite a long period of time, as the history of lower abdominal and pelvic pain for at least two years suggests. The history of five years' sterility might also be explained on this basis. At the present time (June 26, 1939) the abdominal wound has completely healed, the patient's weight has returned to normal and she is menstruating regularly. Tubal pregnancy was made possible through the patency of the abdominal ostium which is so often sealed off in the usual case of tuberculous salpingitis. The probable explanation for the remarkable infrequency of coincidental tubal pregnancy and tuberculous salpingitis has been adequately discussed by Stevenson and Wharton. In the cases which have been reported the condition occurred more commonly in the left tube. This also applies to our case. It is also noted in our case that pregnancy occurred in the lumen of the tube closely adjacent to the tuberculous process as also happened in four of the reported cases, rather than at the ostium, or attached to the fimbriae or an ovary.

REFERENCE

Stevenson, C. S., and Wharton, L. R.: Am. J. Obst. & Gynec. **37**: 303, 1939.

CARCINOSARCOMATODES OF THE UTERUS*

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CARCINOMA of the uterus, while not a rare condition, occurs but once among each 670 women registering at the Mayo Clinic. Sarcoma of the uterus, on the other hand, is rare, accounting for only 2.5 per cent of malignant lesions of the uterus. The coexistence in the same uterus of two tumors, one an adenocarcinoma, the other a sarcoma, is an unusual coincidence, having been reported in about twenty instances only. Carcinosarcomatodes of the uterus is the term used to designate a single neoplasm, having the morphologic features of carcinoma and sarcoma. The entire literature on this pathologic curiosity consists of six individual case reports.

HISTOGENESIS

Sarcoma of the uterus may arise in the myometrium or in the endometrium. In the myometrium it may be primary or originate in a pre-existing leiomyoma. Theoretically it might arise from smooth muscle tissue, connective tissue, or endothelium of blood vessels. Many authorities, among them Ewing, have expressed the belief that all sarcomas of the myometrium are of myogenic derivation. Sarcomas of the endometrium are always primary and are generally conceded to be derived from the stromal cells. Adenocarcinoma of the fundus of the uterus is derived from the endometrial glands.

The histogenesis of carcinosarcomatodes is not at all well understood. Ewing summarized the existing theories as follows: (1) A carcinoma and a sarcoma begin as separate tumors and later one invades the other. (2) At the point where a sarcoma reaches the endometrial surface, a carcinoma develops secondarily. (3) A common irritant produces neoplasia of both epithelial and connective tissue elements.

PATHOLOGY

Sarcoma of the endometrium occurs in two forms: the polypoid and the diffuse; no cases of carcinosarcomatodes of the latter type have been described. The lesions are vascular with a smooth surface as contrasted with the shaggy appearance of adenocarcinoma of the uterus. For the sarcoma, round, oval and spindle-cell varieties, alone or mixed, have been described. Giant cells have been encountered occasionally. Mitotic figures and other features of malignancy are present. The blood vessels are numerous, thin-walled and occasionally are invaded by sarcoma cells. Evans has derived a mathematical formula for the activity of growth of uterine sarcoma; he based his data on the number of mitotic figures per cubic millimeter of tumor tissue. He found a direct relation between the number of mitotic figures and the duration of life after operation. The carcinomatous portion of the lesion manifests itself by atypical glandular proliferation in the depths of the polyp or on the free surface of the latter, as in the case we are about to report. Multiple mitotic figures, prominent nucleoli and lack of differentiation are usually marked features. The relative malignancy of these lesions cannot well be determined because of insufficient data on the small number of cases reported. However, we do know that primary uterine sarcoma is much more malignant in its course than the so-called secondary variety. Kimbrough stated that three-year cures were obtained in 15 per cent of the cases of primary uterine sarcoma. In contrast to this, Masson reported 70 per cent

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of cures in a series which included mainly sarcoma originating in fibroids. It is evident, therefore, that the prognosis is three or four times better in the secondary than in the primary type, which includes the tumors under consideration.

CLINICAL FEATURES

The clinical features of carcinosarcomatodes are not characteristic. Most of the recorded examples occurred among nulliparous patients after the menopause; a similar observation was made in cases of endometrial sarcoma. Bleeding was a constant feature and appeared to be more persistent and profuse than in cases of carcinoma of the fundus of the uterus. There were no other noteworthy features.

In 1932 it was stated by Wolfe that a diagnosis of endometrial sarcoma is made from endometrial scrapings in about 50 per cent of the cases.

REPORT OF A CASE

A married, white nullipara, aged 29 years, first registered at the clinic Feb. 8, 1923. An operation for perirectal fistula was performed. Her family history and personal history were not significant. Appendectomy had been performed five years previously. Menses were recorded as being regular and normal. Between the years 1923 and 1928 she was seen at the clinic on several occasions and received treatment for pulmonary tuberculosis with good result. On her fifth visit to the clinic, Oct. 1, 1934, her complaint was menorrhagia of six months' duration, which was associated with prolonged menses. For two months drainage of a brownish material had occurred intermenstrually. Dilatation and curettage was carried out Oct. 4, 1934, and the patient was given a half of a menopausal dose of radium. The pathologic diagnosis from the scrapings was endometritis.

On April 22, 1938, the patient again returned to the clinic complaining of a bloody vaginal discharge which had been present continuously for three weeks. There had also been pain of intermittent character in the right lower quadrant of the abdomen and in the lumbar region. She attributed her present complaints to an automobile accident which had occurred immediately prior to the onset of the vaginal bleeding.

Physical examination gave essentially negative results except that a small polypoid-appearing mass about 2 cm. in diameter was presenting at the external os. It had the glossy appearance of placental tissue. The possibility of an incomplete miscarriage was considered, but the cessation of menstruation two years prior to this time made pregnancy only a remote possibility.

April 23, 1938, the cervix was dilated and a curettement of the uterine cavity was carried out. Microscopic examination of the tissue removed revealed fibrosarcoma. Hysterectomy was advised but because of the patient's indecision it was delayed three weeks. On May 13, a radical total abdominal hysterectomy with removal of both tubes and ovaries was performed. The abdominal exploratory procedure did not reveal any abnormality except that the gall bladder was thin walled and contained multiple stones. There was no noticeable change in the lymph nodes indicating spread of the malignant process. An uneventful convalescence followed and the patient was able to be dismissed from the hospital on the twelfth day after operation and from the clinic on the seventeenth day.

Study of the organs removed revealed both tubes and ovaries to be normal. The uterus measured 6 by 5 by 4 cm. and contained multiple mural leiomyomas measuring as much as 3 cm. in diameter. On the endometrial surface, immediately above the internal os, there was a sessile polyp about 5 mm. in diameter which was soft and smooth; on section, it proved to be very vascular. Microscopically it presented the unusual combination of sarcoma and carcinoma. No other lesions were in evidence in the endometrium, which grossly was atrophic.

On her last admission, March 3, 1939, the patient stated that she had been well for eight months following her last operation. On Jan. 10, 1939, there had suddenly developed pain in the region of the left shoulder; the pain had extended down the left arm. Ten days later pain of a similar character and distribution developed

in the right shoulder. One month later numbness was noticed in the lower extremities. This numbness had gradually "ascended" to involve the entire surface of the body below the line of the clavicle. Physical findings were those of a transverse myelitis at the level of the first thoracic vertebra with sensory and motor paralysis, below the lesion. Roentgenologic examination of the spinal column gave negative results but spinal puncture revealed a complete spinal subarachnoid block.

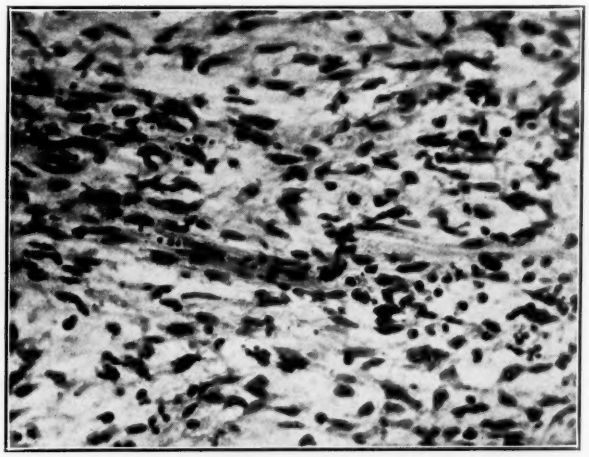

Fig. 1.—Section from operative specimen of tumor of spinal cord, showing a metastatic fibrosarcoma; one may note absence of carcinomatous elements (×240).

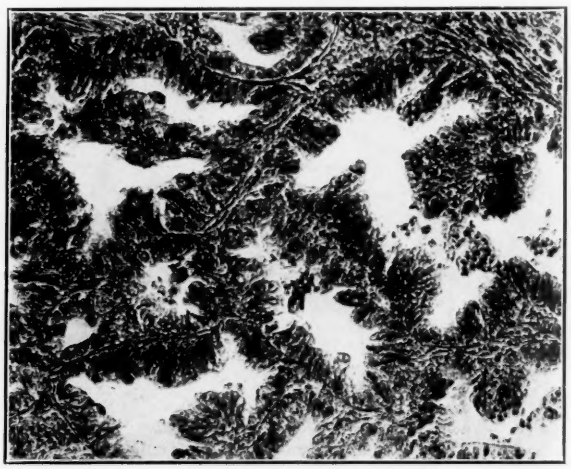

Fig. 2.—Uterine polyp showing carcinomatous element (×200).

At operation on March 15, 1939 Dr. Adson performed a laminectomy and curetted away from the first thoracic lamina, a tumorous mass of tissue that was found to be compressing the spinal cord. Microscopic examination of the tissue removed revealed a fibromyxosarcoma (Fig. 1). Following operation, some subjective relief was temporarily obtained, and a course of roentgen therapy to the spinal column was begun. This had to be discontinued because of persistent nausea. Rapid failure ensued with abdominal distention, weakness and drowsiness, and death occurred on April 17, 1939. Necropsy disclosed widespread skeletal and visceral metastases of sarcomatous type.

Microscopic study of sections of the polyp revealed regions of glandular formation, manifestly carcinomatous (Fig. 2). Arrangement was atypical with occasional papillary infolding. Under the high power objective the cells were seen to be of a columnar type with large nuclei and nucleoli. The nucleonucleolar ratio of MacCarty indicated malignancy. An average of five mitotic figures was seen in each field viewed at a magnification of 500 diameters. The stroma of the polyp was made up of oval and spindle cells and an occasional giant cell was seen. The nuclei of these

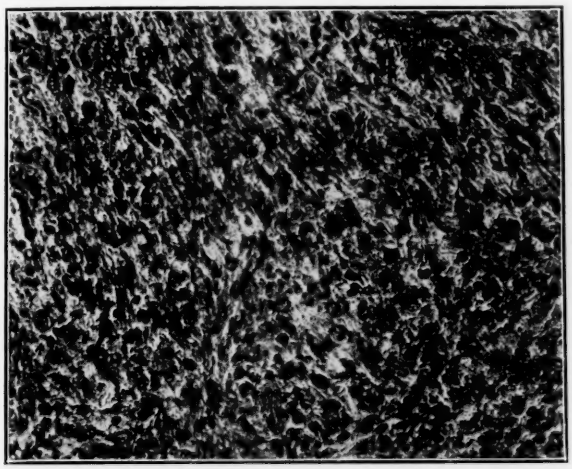

Fig. 3.—Stroma of polyp showing sarcomatous elements (×300).

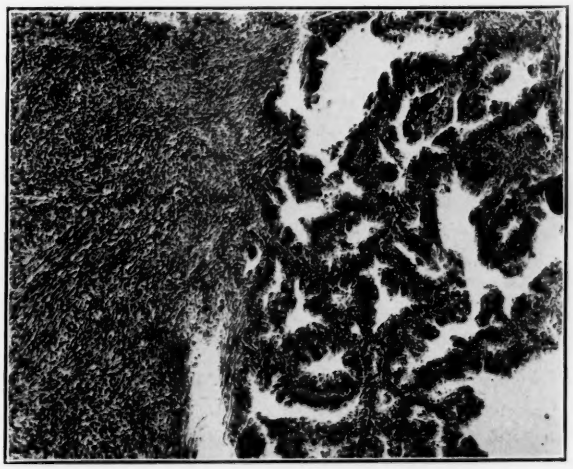

Fig. 4.—Section through polyp showing junction of sarcomatous and carcinomatous portions (×75).

cells were large and dark staining. Mitotic figures were numerous; an average of 6 was seen in each field viewed with the high power objective. Vascularity was marked and the vessels were, in most instances, lined by a single layer of endothelium. No vascular invasion by tumor cells was observed in any section (Fig. 3).

In certain parts of the polyp (Fig. 4), there seemed to be a definite line of demarcation between sarcoma and carcinoma. In other parts the appearance was that of isolated carcinomatous glands dipping down into a sarcomatous stroma. The endometrium in other regions presented varying degrees of atrophy and cystic forma-

tion. Sections through the fibromyomas revealed no evidence of sarcomatous transformation. The tubes and ovaries were not unusual microscopically.

COMMENT

Hysterectomy was indicated when the presence of a malignant lesion was established at the time of curettement. In instances in which the procedure cannot be carried out immediately, as in this case, it is the experience of one of us (Dixon) that hysterectomy should be delayed several days rather than two or three days following curettement, the reason being that the lymphatics surrounding the cervix are apparently the site of origin of an infectious process which may result in extensive and fatal peritonitis if hysterectomy is performed too soon after curettement. Therefore, the belief is here expressed that if hysterectomy is indicated after curettement and it cannot be carried out immediately, which is the ideal time, then it should be delayed for at least ten days for the purpose of allowing any infectious process in and around the cervix and uterus to subside.

Pathologically this case is of exceptional interest because of the unusual "mixed" character of the malignant lesion. The "selective" nature of the metastasis, in which sarcoma alone was found, indicates that the sarcoma had metastasized by the blood stream before the carcinoma had begun to spread. This observation is in keeping with the relative activity of these two types of malignant lesions in connection with the endometrium.

So far as we know this is the seventh case of carcinosarcomatodes to be reported in the literature.

REFERENCES

(1) *Evans, Newton:* Surg. Gynec. Obst. **30:** 225, 1920. (2) *Ewing, James:* Neoplastic Diseases, Philadelphia, 1922, W. B. Saunders Company, pp. 267, 268. (3) *Kimbrough, R. A.:* Am. J. Obst. & Gynec. **28:** 723, 1934. (4) *Masson, J. C.:* Ibid. **5:** 345, 1923. (5) *Wolfe, S. A.:* Ibid. **23:** 232, 1932.

Relevant Articles Not Referred to in Text

DerBrucke, M. G.: Am. J. Obst. & Gynec. **26:** 457, 1933. *Goldstine, M. T.:* Ibid. **30:** 143, 1935. *Spencer, H. R.:* Tr. Obst. Soc. London **47:** 338, 1905. *Williams, J. W.:* Am. J. Obst. & Dis. Wom. **29:** 721, 1894.

Bocchini, Adriano: Benign Cutaneous Induration of the Newborn (Pseudo-Scleroderma), Arch. di ostet. e ginec. **2:** 52, 1938.

During the last few years there has been described a particular affection of the skin of the newborn. It is more commonly designated as benign subcutaneous induration of the newborn, or pseudoscleroderma.

It is characterized by zones of cutaneous infiltration varying in size from a small nodule to an area as large as the palm of the hand. The areas are slightly elevated, irregular, and of a deep wine red color. They show a ligneous resistance, and prolonged pressure will not cause pitting. The surface at times resembles that of a lemon peel. The condition successively regresses; the color becomes paler and the zone of induration reduces in extent until it entirely disappears.

These infiltrations appear immediately after delivery or within a few days after, rarely after the second week. Sites of predilection are in the regions of the face, deltoids, back, and buttocks.

The disease may last from a few weeks to a few months, always ending in a spontaneous cure. Progress and growth of the infant are not affected.

There are numerous theories for its histogenesis, and though none is satisfactory, the process fundamentally concerned is the saponification in situ of neutral fats in the subcutaneous tissues.

The diagnosis of this condition is not difficult and the author presents the differential points which contrast the condition from true scleroderma.

A. A. Marchette.

TUBERCULOUS ENDOMETRITIS

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THE case herein reported was found accidentally to have genital tuberculosis during the course of a routine investigation of sterility.

R. E., female, white, aged 30 years, was referred on May 20, 1936, for the study of primary sterility of ten years' duration. Her previous medical, surgical, and family history was negative. Catamenia began at 14, recurring regularly every twenty-eight days for a period of three days. Eight years ago the menstrual flow diminished to that of a stain but the regularity of the cycles persisted. About that time her weight rose from 120 to 146 pounds.

Six years ago, after four years of sterility, a physician was consulted for the first time. The Rubin insufflation test revealed the tubes to be patent. The condom specimen was reported as normal. Following this investigation the patient was hospitalized, the cervical canal dilated and a stem pessary inserted. No curettage was performed. The stem pessary was removed a few months later.

Three years later she consulted another physician for the persisting sterility. A lipiodol hysterosalpingogram showed a uterus of normal size, both tubes patent to fimbriated ends. Twenty-four-hour plate showed encapsulated oil at both fimbriated ends.

In 1935 she returned because of a continuance of the sterility and hypomenorrhea. No genital pathology could be detected. Thyroid extract was prescribed and shortly afterwards the menstrual flow became heavier. Since then her cycles have been normal in every respect. The following year she was referred to me for a more complete study of the sterility.

Physical examination (May 20, 1936) revealed a well-developed and well-nourished female, height 60¼ inches, weight 146 pounds. Obesity was noted particularly about the shoulders and the trunk. Hair was brown and dry, and distributed normally except for slight excess on the legs. The skin was coarse and thickened. The thyroid was not enlarged. The pupils were equal, regular and reactive. There was no exophthalmos. The teeth were not spaced and were well preserved. The tongue exhibited marginal corrugations due to impressions of the teeth. The neck was short and thick. The breasts were somewhat pendulous, free of masses, and no secretion could be expressed from the nipples. The heart and lungs were normal. Blood pressure 124/78. The abdomen was not distended. No organs or masses were felt. The extremities were normal except for short stubby fingers. The reflexes were normal.

Vaginal examination revealed labia minora slightly hypertrophied. The clitoris was not enlarged. The introitus admitted two fingers. The vagina was roomy. The uterus was normal in size, shape, and position, freely movable and not tender. The ovaries were not enlarged. The tubes could not be palpated. A normal nulliparous cervix was seen on speculum examination.

Clinical Laboratory Data.—Basal metabolism (Jones) minus 10 per cent; blood Wassermann, negative; blood count: Hg was 82 per cent; red blood count, 4.5 million; white blood count, 5,400; polymorphonuclears, 48; lymphocytes, 51; monocytes, 1.

Tubal insufflation done on ninth day of the menstrual cycle; 280 c.c. of CO_2 gas was introduced. The pressure rose at first to 160 mm. Hg and then dropped to 80 mm. Hg, at which level the flow of gas continued without obstruction. Pain was experienced in the right upper quadrant. Fluoroscopic examination revealed an elevation of the right leaf of the diaphragm.

Postcoital examination (Huhner Test) revealed numerous actively motile spermatozoa one hour after coitus. Many spermatozoa also present in the cervical mucus. No abnormal forms were seen.

Biopsy of the endometrium done on twenty-sixth day of the menstrual cycle. Microscopic examination revealed large fragments of endometrial tissue, with glands elongated, widened, and tortuous. They were lined by a single layer of tall columnar cells taking the acid stain and showing secretory activity. The lining of the glands was thrown up into papillary folds. Surrounding stroma was edematous, congested, and hemorrhagic. This glandular picture was uniform in all sections on the slide. There were several foci present, composed of a central area of necrosis, a collar of lymphatic cells, and giant cells of the typical Langhans type. Ziehl-Nielsen stain failed to reveal any tubercle bacilli. Pathologic diagnosis: Physiologic hyperplasia of the endometrium corresponding to the late premenstrual phase. Tubercles suggesting tuberculosis of the endometrium (Fig. 1). The pathologic report clearly showed that ovulation had definitely occurred, but it threw a new light on the cause of the sterility by revealing the unsuspected presence of tubercles.

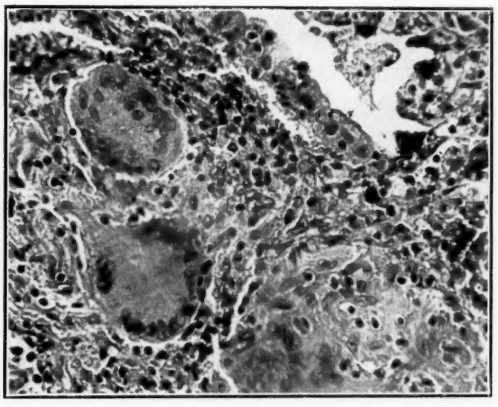

Fig. 1.

Are these tubercles the result of tuberculosis? It is well known that tubercles may develop in the endosalpinx following lipiodol instillation. But there is no record that the endometrium is similarly affected. The periodic monthly deciduation of the uterine mucosa would hardly facilitate the formation of foreign body granulomas in the endometrium. Nevertheless, to exclude this possibility, the giant cells were searched for foreign bodies, including a polariscopic examination for doubly refractile fat. No foreign bodies were found.

To establish the diagnosis of tuberculosis beyond doubt, additional data were necessary. The family history was gone into in great detail but no instance of tuberculosis was brought to light. A Mantoux test, using old tuberculin (O.T.) was strongly positive in dilutions down to 0.000001. (The average adult may react to a dilution of 0.001 old tuberculin. A positive reaction to weaker dilutions may be interpreted as an indication of an active tuberculous infection.)

Radiographic examination of the chest (Dr. M. Friedman) on March 17, 1937, did not show any pathologic changes in the lungs. There was no evidence of a recent or old tuberculous process. The heart was approximately normal in size, shape, and position.

Another biopsy of the endometrium was done on the twenty-fifth day of the menstrual cycle. The specimen was divided into two portions, one of which was run through for microscopic examination, and the other was injected into a guinea pig. The histologic picture corresponded to that observed previously. The guinea pig was killed after six weeks, but no evidence of tuberculosis was found.

Slides of both biopsies were sent to Robert T. Frank who stated that "there is no question but that you are dealing with a tuberculosis of the endometrium."

Subsequent Course.—An attempt was made to increase the patient's resistance to the tuberculous infection by vaccination. She was given subcutaneous injections of old tuberculin twice weekly from March 22, 1937, to July 26, 1937, commencing with 0.15 c.c. of a 1:1,000,000 dilution and gradually increasing the amount until the patient could tolerate a dose of 1 c.c. of a 1:1,000 dilution. Throughout this period she exhibited no general reaction or marked local reaction to the injections. The Mantoux test was repeated in September, 1937. This time the reactions were within the normal range as she was positive to the 0.001 dilution and negative to the 0.0001 dilution of old tuberculin.

The endometrial pathology, however, remained unchanged, for another biopsy on Oct. 15, 1937, was reported by Dr. Ehrlich to exhibit lesions closely resembling the tubercles found in previous biopsies.

On June 7, 1938, the patient was admitted to Lebanon Hospital for a thorough curettement. Her physical status was no different than when examined a year previously. Under anesthesia the uterus and adnexa were carefully palpated, but no distortion or enlargement could be felt. The endometrium was removed by sharp curette. The specimen was divided into two portions, one for routine microscopic examination and the other for guinea pig inoculation. The pathologic report again revealed typical tuberculous granulomas. The guinea pig was autopsied after six weeks, and this time tuberculous foci were found in the diaphragm, liver, and spleen.

The diagnosis of tuberculous endometritis was now definitely established.

The patient was last seen Feb. 15, 1939, still complaining of sterility. She is in apparent good health and exhibits none of the clinical features of an active tuberculous lesion such as weight loss, increased pulse rate, and rise in afternoon temperature. Her menses are regular and normal in character. The vaginal discharge is scanty.

DISCUSSION

Primary tuberculosis of the endometrium is a most unusual entity. Gordeler[1] (quoted by Norris) in 1913 found 1 case in 4,620 post-mortem examinations in a hospital for tuberculous patients. Norris[1] never saw a case of proved tuberculous endometritis in which the tubes were not involved. On the other hand, Siddall[2] recently reported a case accidentally discovered by curettage in which the lesion was found to be limited to the endometrium when hysterectomy and bilateral salpingectomy were performed.

In view of the rarity of primary tuberculous endometritis and for want of more complete histologic studies of the uterus and tubes, it is quite likely that the patient here reported has a coexisting microscopic tuberculous lesion in the tubes. The persisting sterility also favors this assumption. It is doubtful whether the scattered tubercles seen in the secretory endometrium could prevent nidation once impregnation occurred, but fertilization of the ovum could be inhibited by a tuberculous endosalpingitis.

The treatment of choice for tuberculosis of the uterus is hysterectomy and bilateral salpingectomy. It offers the best prognosis particularly when the disease process is limited to the uterus and tubes. Jameson,[3] in an excellent review of genital tuberculosis, states that most authorities prefer radical surgery even in the presence of more extensive pathology.

X-ray irradiation has also been tried, but it is most effective in the treatment of sinuses which may develop following operation. Mensing[4] reported a case of a patient with tuberculous endometritis who was treated with 1200 mc.hr. of radium, but he failed to prove whether a cure occurred by performing a subsequent curettage for further histologic study of the endometrium.

Curettage alone cannot be expected to cure primary tuberculosis of the endometrium, because the disease usually involves the myometrium as well. It is still less effective in the treatment of secondary tuberculous endometritis. It

may even be fraught with danger for cases have been reported in which tuberculous peritonitis[5] or acute miliary tuberculosis[6] have developed after this procedure.

Some authorities advocate a "hands-off" policy. The apparent good health of the patient described above would seem to justify this attitude. Nevertheless a quiescent tuberculous focus too often becomes activated under conditions outside our control. This possibility alone warrants the radical removal of the uterus and tubes. It is to be regretted that the strong maternal instinct and the sense of well-being enjoyed by my patient have caused her to reject any treatment which would prevent conception.

SUMMARY

A case of sterility due to tuberculosis is described in which a tuberculous endometritis probably secondary to tuberculosis of the tubes was accidentally discovered by biopsy of the endometrium. The diagnosis was established by inoculation of a guinea pig with endometrial tissue. The patient has been under personal observation for over two and one-half years and shows no ill effects of the disease.

While conservative treatment has been followed in this case, hysterectomy and bilateral salpingectomy should be the method of choice.

REFERENCES

(1) *Curtis, A. H.:* Obstetrics and Gynecology **2:** Philadelphia, 1933, W. B. Saunders Co., pp. 558-598. (2) *Siddall, R. S.:* J. Michigan Med. Soc. **35:** 561, 1936. (3) *Jameson, Edwin M.:* Am. J. Obst. & Gynec. **27:** 173, 1934. (4) *Mensing, K.:* Zentralbl. f. Gynäk. **60:** 1210, 1936. (5) *Diethelm, Martin W., and Ramsey, Thomas L.:* Ibid. **30:** 420, 1935. (6) *Bungeler, W.:* Frankfurt. Ztschr. f. Path. **47:** 313, 1934.

A DEFORMED PELVIS DUE TO CLEIDOCRANIAL DYSOSTOSIS*

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CLEIDOCRANIAL dysostosis is a rare disease, characterized by delayed or incomplete ossification of the skeleton, usually affecting most of the bones formed from membrane. We have observed a mother and her child, who had many deformities due to this dysostosis. The mother had a deformed pelvis.

Mrs. S. P., white, had had two pregnancies. The first infant was delivered by midforceps, after a second stage of labor lasting eight hours. He weighed 3,510 gm. Death occurred twenty-four hours later from an intracranial hemorrhage. Tears of the right and left tentorium cerebelli were found at autopsy. There was no evidence of cleidocranial dysostosis.

She was under our care during the second pregnancy. Her last menses began on Aug. 27, 1937. She was 25 years of age, and the youngest of eleven children. There was no history of any bone abnormalities in the family. She was told that her fontanels had been open for several years.

The permanent teeth had been extracted because they erupted late and soon became carious. One incisor had recently erupted. Her skull had a deep frontal groove and prominent frontal and parietal bosses. The nose was of the "saddle" type. Her skeletal measurements are presented in Table I. The ribs had no evidence of a rachitic rosary. The lateral half of the right clavicle and the lateral third of the left clavicle could not be palpated. The tibiae were small, but normal in contour.

The "rhomboid" of Michaelis was triangular. The pubic arch was narrow. No separation of the symphysis pubis could be felt. The posterior surface of the symphysis seemed more angular than normal. The entire linea terminalis could be

*For lack of space, the review of the literature is included only in the author's reprints.

palpated. It extended straight backward on each side with slight concavity. The ischial spines were "hooked." The sacrum was flat from side to side, and the promontory seemed to "overhang" the inlet.

Her blood calcium was 9.4 mg. per 100 c.c.; blood Wassermann test was negative. A slight hypochromic anemia was present.

A living male child, weighing 4150 gm., was delivered on May 23, 1938, by a low cervical two-flap cesarean section. We measured the transverse diameter of the pelvis with a DeLee pelvimeter (Table II) during the operation, but we were unable to measure the conjugata vera accurately, due to a "false promontory" of the sacrum.

Both clavicles of the infant were abnormal. The right clavicle was about 1 cm. in length, and the outer two-thirds was absent. The left clavicle was slightly longer. The sagittal and frontal sutures were wide open, but there was no bulging of the fontanels. The frontal and parietal bosses were prominent. Anyone unfamiliar with this disease might, at first glance, make a diagnosis of hydrocephalus. In other respects the infant appeared normal.

The pelvis of our patient was reduced in all of its dimensions except the anteroposterior diameter of the outlet (Table II). The inlet was "heart shaped"; the posterior surface of the pubis was angular; and the subpubic angle was acute. It closely resembled that of a generally equally contracted rachitic pelvis.

TABLE I. SKELETON MEASUREMENTS

Weight	35.7 kilos
Height	137.0 cm.
Circumference of skull	22.4 cm.
Humerus	26.0 cm.
Ulna	21.0 cm.
Femur	39.5 cm.
Tibia	33.0 cm.
Xiphoid to symphysis	28.0 cm.

TABLE II. PELVIC MEASUREMENTS

Interspinal	21.0 cm.
Intercristal	22.5 cm.
External conjugate	18.0 cm.
Diagonal conjugate	10.0 cm.
Transverse of outlet	7.5 cm.
Anteroposterior of outlet	12.0 cm.
Posterior sagittal	8.25 cm.
Transverse of inlet*	10.50 cm.
True conjugate*	9.25 cm.
Transverse of inlet†	10.00 cm.

*By roentgenogram.
†At operation.

COMMENT

Possibly the second infant of our patient could have been delivered through the pelvis, but in view of her previous difficult labor, we felt that delivery by a hysterotomy was indicated. The infant's weight (4150 gm.) was greater than any yet reported in the literature on this subject. Also our patient was shorter (137 cm.) than the patients reported as being delivered without difficulty.

The type of pelvis found in women with cleidocranial dysostosis is still a matter open for further study. More patients must be examined by the Thoms method or by the stereoscopic method of Caldwell and Moloy, before one can definitely answer this question.

PURPURA RHEUMATICA COMPLICATING THE PUERPERIUM

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UP UNTIL July, 1937, there have been approximately eighty cases of purpura hemorrhagica complicating pregnancy and the puerperium reported in the literature. Of all these cases only one, which was reported by Barnes in 1867, showed rheumatic symptoms, and in this case they were rather indefinite.

Mrs. E. B., aged 22 years, white, gravida ii, para i, Kahn-negative, was admitted to the ante-partum clinic May 25, 1938. Last menstrual period was Dec. 4, 1937, and expected date of confinement was Sept. 11, 1938. The family history was essentially negative.

The patient had had the usual childhood diseases, no diphtheria, scarlet fever, or other serious illness. Appendectomy several years previously. She denied venereal infections.

She was delivered in 1937 of a full-term infant. At this time she had a mild toxemia, secondary anemia, and a possible attack of malaria fever.

Menstrual history was perfectly normal, beginning at the age of 13 years, regular every twenty-eight days, of five days' duration, and the flow had always been normal.

When seen in the clinic, the patient's physical examination was normal, except for slight decay of the teeth and a systolic murmur over the apex. At this time she was approximately five months pregnant, and showed a red cell count of 2,312,000 and hemoglobin of 8 gm. per 100 c.c. of blood. Iron at this time was given for the anemia. During her ante-partum period her blood pressure varied from 110/70 to 120/95, and she showed a net gain of 7.5 pounds. Early in August she complained of pain and swelling in her left ankle, for which she was given salicylates and hot foot baths, which gave her relief. Otherwise her ante-partum course was perfectly normal.

On Sept. 30, 1938, the patient was admitted to John Gaston Hospital in the first stage of labor. On admission she was at full term and the cervix was beginning to dilate. Her blood count at this time showed 3,100,000 red cells, hemoglobin 10 gm., and 8,800 white cells. The differential count was normal and the urine was negative. After a slightly prolonged labor of twenty-five hours and fifty minutes, she delivered a living normal full-term infant spontaneously. The bleeding at the time of delivery was very slight. Her puerperium was normal until the third day of October when her temperature suddenly rose to 101.6° F. and her pulse to 136. At this time maculopapular purpuric spots, which varied from 1 mm. to 3 cm. appeared suddenly over her shoulders, buttocks, legs, torso, plantar and dorsal surfaces of the feet, face, and even on her scalp. These spots were purple in color, slightly tender, and did not disappear on pressure. The lochia at this time were normal and the blood pressure 118/70. On October 4, these areas had increased in size and some of them had coalesced. The left ankle was swollen, red, and very tender to movement and pressure. Over the metacarpals of the right hand was an area of edema, redness and tenderness. Both shoulders and right ankle were extremely tender and painful to both passive and active motion. There was a blowing systolic murmur over the valvular areas, transmitted to the vessels of the neck. The spleen was enlarged to 4 cm. below the left costal margin, and the liver was about 1.5 cm. below the right costal margin. The uterus was firm, and three fingers below the umbilicus. The blood count at this time had dropped to 1,450,000 red cells, hemoglobin 7 gm., 2,250 white cells,

and the platelet count was found to be 43,500. The differential count showed 82 polymorphonuclear leucocytes, large lymphocytes 6 per cent, small lymphocytes 12 per cent. No malarial organisms were found, coagulation time was one minute, and the bleeding time two and one-half minutes. Blood calcium 8.5 mg. per 100 c.c. of serum, and the blood culture was negative. The urine at this time was negative except for an occasional red blood cell.

The hemorrhagic areas continued to increase in size and number, especially around the joints. In the areas which came in contact with the bed, the hemorrhagic spots became confluent, assumed a bleb-like appearance from which exuded a bloody serum, and these areas were surrounded by a zone of erythema. These areas were not tender to pressure, but did itch and the soles of the feet had a burning sensation. The mucous membranes at no time showed any involvement, and the lochia did not increase in amount.

Immediately upon the appearance of the purpuric areas the patient was given a blood transfusion of 500 c.c., 5 c.c. of calcium gluconate twice a day hypodermically, 5 c.c. of hemostatic serum intramuscularly every four hours, and vitamins were given in the form of yeast and a high vitamin diet. The purpuric areas continued to enlarge, and the patient was given another transfusion of 500

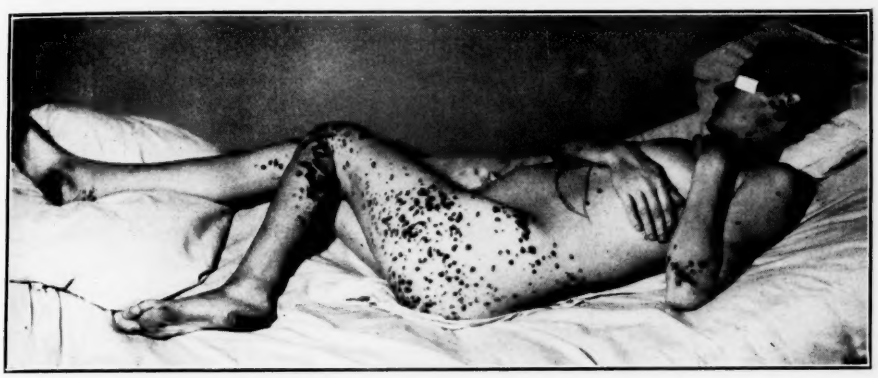

Fig. 1.—Showing patient at the onset of the attack of purpura rheumatica.

c.c. of whole blood the day after the appearance of her symptoms. On October 6 and 7, her spleen was irradiated. Following this treatment the bleeding time increased to three minutes and the blood count showed 2,200,000 red cells, 8.1 gm. of hemoglobin, and 11,200 white cells. The platelet count also increased to 150,000.

It was suggested at this time that the purpura was due to an allergic condition of unknown origin. Therefore, the patient was given some of each drug that she had taken previously, without any flare-up of her condition. Due to information obtained from the husband, the etiologic factor was determined as due to a low calcium and vitamin diet during the ante-partum period, along with the possibility of toxemia.

Under the treatment as outlined above, the edema and the tenderness of the joints disappeared and no new spots appeared. The old purpuric lesions gradually dried up, and became covered with a black purplish crust. The temperature continued to run a slight septic course betwen 99° and 100.6° F. The pulse returned to 90, and remained approximately at that rate. The patient was given another transfusion of 750 c.c. of whole blood one week after the appearance of the purpura. The platelet count rose to 159,500 and remained comparatively stationary. The red count increased to 3,860,000 with 9 gm. of hemoglobin. The general condition of the patient continued to improve, and on October 16, she was discharged from the hospital.

The baby was perfectly normal and well. There were no signs of any purpura and the weight curve was practically normal.

The patient returned for a post-partum check-up examination on Nov. 12, 1938. At this time all of the lesions were completely healed, but showed some scarring, particularly around the hips. There had been no new lesions. The spleen was still large and the liver was palpable about 1 cm. below the right costal margin. The pelvic organs were normal, and there was a moderate amount of mucopurulent leucorrhea. The blood count showed 3,400,000 red cells, 8.8 gm. of hemoglobin, 5,200 white cells, and 180,000 platelets. The tourniquet test was normal and her general condition was good. The baby was tested for any signs of hereditary purpura and showed both a normal blood picture, and normal bleeding and coagulation times.

The etiologic factors in this case were thought to be a vitamin and a calcium deficiency during the ante-partum period associated with a mild toxemia of pregnancy.

The authors wish to express their appreciation to Dr. J. L. Scianni for the illustrations, and the cooperation of the attending, house, and nursing staffs of the Maternity Pavilion of the John Gaston Hospital for their cooperation in this case.

MONOAMNIOTIC TWIN PREGNANCY WITH LIVING INFANTS

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THE following case is reported because of the relative rarity of twins developing in one amniotic sac and because of the greater infrequency of survival of both infants. Monoamniotic twins occur once in approximately 10,000 pregnancies. Quigley, in 1935, reported the only case in the American literature in which even one infant of a monoamniotic twin pregnancy survived. In his comprehensive review of the 109 cases previously reported, both twins had lived in only 17 instances. He found the fetal death rate of monoamniotic twins to be 68 per cent. Since Quigley's presentation, two additional cases have been reported in the United States. In neither case did both twins live.

As far as we have been able to determine, the following case is the first in the American literature in which both infants of a monoamniotic twin pregnancy have survived.

D. G., colored primipara, aged 17 years, was admitted to Gallinger Municipal Hospital on April 12, 1939, with ankle edema of three weeks' duration, blurring of vision for three days, occasional abdominal cramps, and a blood pressure elevation of 150/120. Her last normal menstrual period began Aug. 15, 1938, making the expected date of confinement May 22, 1939. Quickening occurred in December, 1938. Family history was of interest in that the patient's maternal grandmother had twin boys who were reported as identical in appearance. The patient's husband's great-grandmother gave birth to twin girls who were said to be identical.

The patient was a well-developed, well-nourished, rational, young colored woman near term, and not in labor. Eye grounds showed some arteriospasm. Blood pressure was 150/120. Abdomen showed a fairly tense ovoid tumor of a pregnancy at or near term. Fetal head was in the left upper quadrant of the abdomen. Small parts were palpable on the right. Fetal heart sounds of approximately the same rate, 150 to 160 per minute, were heard in the left upper and left lower quadrants of the abdomen. Multiple small parts suggested twins, but a confirmatory x-ray plate was not obtained. Pelvic measurements were within normal limits. Extremities showed two plus edema.

Laboratory Findings.—Kahn was negative. Urine showed 5.5 gm. per liter of albumin (Esbach). Blood studies showed hemoglobin 54 per cent, red blood count 3,300,000, white blood count 8,500, urea nitrogen 10 mg. per 100 c.c. blood, sodium chloride 460 mg., and cholesterol 240 mg. per 100 c.c. blood.

With bed rest, sedation, and a salt-free diet, patient showed no improvement in her pre-eclamptic symptoms. On the third day following admission, labor was induced with a hot enema, and a total of six minims of pitocin were given in divided doses. The fetal head was engaged. The membranes ruptured spontaneously half an hour before the onset of active labor. The first stage of labor lasted two hours and thirty-five minutes.

The second stage of labor became complicated by infrequent, weak contractions with the fetal head low in the pelvis in L.O.P. position. Fetal heart sounds, heard at a level with the umbilicus on the left, became too rapid to count. Following a left mediolateral episiotomy, a living, premature, female infant (A) weighing 4 pounds 13¼ ounces (2,187 gm.) was delivered with low forceps. Normal fetal respiration was established within a few minutes following the administration of oxygen to the

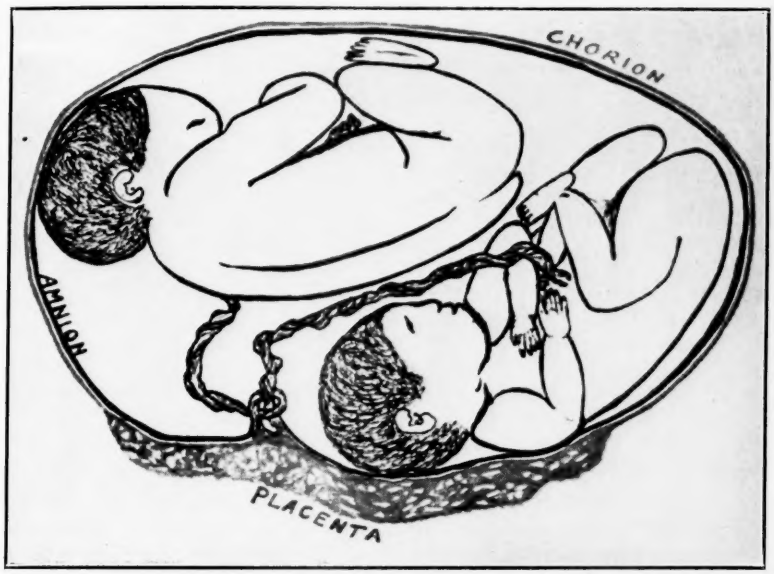

Fig. 1.

infant. Immediately following delivery of the first infant, the left hand of the second baby prolapsed into the vagina. The second infant (B) was found to be presenting in left acromiodorsoposterior position. Immediate podalic version and extraction of a living, premature, female infant, weighing 4 pounds 8¼ ounces (2,047 gm.) was performed. The second infant breathed and cried spontaneously. Duration of the second stage of labor was one hour and forty-five minutes.

The placenta separated spontaneously and was expressed from the vagina thirty-six minutes after the birth of the second infant. Placenta weighed 885 gm. and measured 20 by 16½ by 3 cm. Cord to infant A measured 48 cm.; cord to infant B was 58½ cm. long. Nine centimeters from their placental insertions, the cords formed a true knot. There were anastomoses of the placental vessels going to the cords. Careful examination failed to reveal any evidence suggestive of an amniotic septum between the cords. The maternal surface of the placenta was uniform with normal cotyledons.

The mother's hospital course was afebrile. By the fifth post-partum day, edema had completely subsided, urine showed only a trace of albumin, and the blood

pressure was 140/100. On the eleventh day after delivery, the patient was discharged from the hospital with no edema, a well-involuted uterus, and a blood pressure of 125/85. Both infants received breast milk. When discharged with the mother, infant A weighed 5 pounds 5 ounces (2,410 gm.). Infant B developed a mild upper respiratory infection and failed to gain weight very rapidly. On the thirty-first day after delivery, infant B was discharged from the hospital weighing 5 pounds 6 ounces (2,438 gm.). Except for prematurity, both infants were normally developed. X-ray plates of the infants' chests failed to reveal any abnormality. The finger and foot print patterns of the two infants were entirely different.

Six weeks after delivery, the patient's blood pressure was 128/78 and her pelvic organs were normal. Both infants had gained in weight and appeared healthy.

1843 BURKE STREET, S. E.

PNEUMOCOCCUS, TYPE III, ASSOCIATED WITH PELVIC INFLAMMATORY DISEASE

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A WOMAN with pneumococcus pelvic inflammatory disease was recently observed at Mercy Hospital, and the record of another patient was found in the archives of the University Hospitals. A description of the clinical courses of these two patients seems justified, since Nuckols and Hertig[1] reviewing the reported cases in May, 1938, were able to discover but 77 instances of pneumococcus genital tract infection in women. Of these 77 patients, the infection followed the delivery of a term or near-term baby in 34, was associated with abortion in 17, and was unassociated with any history of a recent obstetric episode in 23. The remaining 3 women, strictly speaking, did not have genital tract infection, but developed pneumococcus peritonitis during pregnancy.

CASE 1.—Mrs. J. W. K., aged 39 years (Hospital No. 1620), was admitted to Mercy Hospital late in the evening of Sept. 17, 1938, complaining of severe abdominal cramps which began twenty-four hours previously. Following onset, the pain gradually became intensified and was accompanied by a diarrhea which developed into a profuse watery discharge. The leucocyte count shortly after onset was 22,000 cells per cubic millimeter. The subcutaneous injection of 0.25 gr. of morphine sulphate relieved the symptoms and the patient became reasonably comfortable until afternoon of the day of admission, at which time a constant abdominal pain accompanied with nausea, but not vomiting, appeared. Two hours before admission the patient suffered a severe, bed-shaking chill. Following the chill, the abdomen became diffusely tender, the lower abdominal cramps became intensified, and the patient passed two watery stools. The catamenia began the day before onset of the present illness. As a young girl, the patient was severely ill with pneumonia, but otherwise had experienced no more than an average amount of illness. One year before admission she suffered from a transient illness characterized by lower abdominal pain and cramps, but recovered after routine treatment for colitis. The last of a series of 4 pregnancies occurred six years ago.

On admission, the patient was acutely ill, with the mouth temperature ranging between 100° and 103° F., the pulse between 80 and 120 beats per minute. On physical examination the nose and throat were normal and the lungs were clear. There was generalized abdominal tenderness with moderate rigidity and no distention. There was no evidence of genital gonorrhea, and cultures from the cervix and

vaginal vault did not contain the diplococcus. The cervix was closed and lateral motion was painful. The uterus seemed to be in midposition and was thought to be slightly enlarged. There was tenderness and induration in each adnexal region, making adequate definition of the ovaries impossible. The hemoglobin was 92 per cent, and there were 38,450 white blood cells per c.mm.

Despite failure to demonstrate the gonococcus, and despite the fact that the patient was prostrated out of proportion to the extent of the clinical and laboratory findings, a provisional diagnosis of acute pelvic inflammatory disease was made.

For the next twelve days, the illness was characterized by pain in the abdomen, headache, severe nausea and vomiting, marked abdominal distention and frequent watery stools, numbering 10 on one day. The leucocyte count fluctuated between 6,700 and 20,900 cells per c.mm. Pus localized in the cul-de-sac, and there was a suggestion of localization in the right adnexal region. On the fourteenth day of the illness, 200 to 300 c.c. of yellowish green pus were drained from the cul-de-sac following puncture, and pneumococcus, Type III, was identified by the usual technique. Despite the drainage, the general condition did not improve, and the patient gradually became worse. She complained bitterly of headache, pain in the abdomen, and was nauseated and vomited frequently. The number of daily liquid stools, however, decreased sharply. On the twenty-sixth day of the illness, the right adnexal abscess was drained through the vaginal fornix of about 200 c.c. of pus. Gradual general improvement followed the second drainage, until the thirty-second day when there was an elevation of temperature and pulse rate. Two days later the pelvis was examined under anesthesia, the draining sinuses were reopened, but no additional pus was found. The general improvement which had been temporarily halted was soon resumed, and on the fiftieth day the fever abated. She was dismissed from the hospital on November 16, the sixty-first day of the illness.

During the first half of the hospital stay, the patient received one and, in several instances, two or three daily intravenous injections of saline and glucose solutions. Supportive measures included sulfanilamide during the early days of the illness, repeated small blood transfusions, vitamin "B," and pelvic diathermy after the acuteness of the condition had subsided. Pneumococcus, Type III, antiserum was not used, since it is generally recognized that, to be effective, it must be administered early. At this time the patient complained of pain in the right and later in the left chest, and on one occasion the lower portion of the chest was strapped with adhesive tape in order to relieve this pain. However, no physical evidence was ever found, indicating involvement of the lungs. Also, there was never any cultural evidence of a pneumococcic septicemia. There was, however, a dry nonproductive cough suggestive of pleural irritation. This cough persisted for a few days, even after discharge, and may have resulted from a common cold.

Two days after discharge the patient was re-admitted, complaining of left-sided abdominal pain and tenderness, and pain in the right chest. A roentgenogram and fluoroscopic examination of the chest revealed no evidence of pulmonary disease and physical examination was entirely negative. There was, however, a recrudescence of fever which persisted for thirteen days and reached a height of 102.2° F. Following eighteen days of normal temperature and pulse rate she was again discharged, after a combined hospital stay of ninety days. She has remained well since, and was examined a month and a half after final discharge from the hospital. At this time the pelvic organs were so completely normal, that no traces of the inflammation could be found. The uterus was normal in size and freely movable, the adnexa were normal, and there was not the slightest evidence of residual induration. The lungs were clear and there was no apparent damage to the heart, which was normal in size and action. Subjectively, the patient had not completely regained her strength, although she was able to carry on average activity.

This patient must be classified with the "localized abscesses" of which Nuckols and Hertig[1] were able to collect 23 examples. It is of interest to note that there was no antecedent history of illness and that the last pregnancy occurred six years ago. There is a history of pneumonia in childhood, but it does not seem logical to

associate this with the present illness. Despite the cough this was presumably an ascending genital tract infection, since physical, roentgenographic and fluoroscopic examinations of the chest were negative.

CASE 2.—Mrs. L. B., aged 20 years (Hospital No. D-9285), was delivered of a 3,470 gm. baby on the Obstetric Service of the University Hospitals, Dec. 31, 1929. The labor was spontaneous, the puerperal course was uneventful except for a fever on the sixth day, and the patient was in good condition with normal pelvic viscera at the time of discharge on the sixteenth post-partum day. A gradually increasing, constant, right lower quadrant pain began about two weeks after discharge, to be followed one week later by daily, afternoon attacks of sharp, severe pains in the same region. There was some burning and smarting on urination, but the patient was uncertain as to the presence of fever, although she admitted that she perspired a great deal at night.

On re-admission, Feb. 18, 1930, the patient obviously was ill. There was no evidence of pulmonary or upper respiratory tract disease. The cervix was closed and the uterus was displaced toward the left by an orange-sized mass. There was tenderness and induration in the left adnexal region. During the hospital course, the temperature ranged from 99.0 to 102.0° F. and the pulse from 90 to 110 beats per minute. Weakness and listlessness were marked. The white cell count, which was 14,900 per c.mm. on admission, gradually rose during three weeks to 26,000. The patient was treated with heat and foreign protein, and twenty-one days after re-admission the right adnexal mass was drained through the vaginal fornix of about 250 c.c. of greenish pus. Pneumococcus, Type III, was cultured from the pus. On the day following operation, there was very little drainage from the abscess, the pulse rate rose to 140 to 150 beats per minute, and it was obvious that the patient had a spreading, generalized peritonitis. The blood was cultured at this time and a Type III pneumococcus was recovered. She died March 16, 1930, five days after operation and twenty-seven days after re-admission. Post-mortem examination of the abdomen revealed a generalized peritonitis, and pneumococcus, Type III, was cultured from the peritoneal exudate. Although the chest was not examined post mortem, it is doubtful if the patient had any lung involvement, since there were no pulmonary symptoms or signs during the clinical course.

Although this patient experienced comparatively good health for the month following labor, the genesis of the infection presumably dates from that time. She should, therefore, be added to that group of 34 recorded cases which followed pregnancy. In all probability this was also an ascending genital tract infection, since there was neither history, symptom, nor sign of any antecedent infection of consequence.

DISCUSSION

Nuckols and Hertig[1] and others, insist that the idea of ascending origin of pneumococcus genital tract infection cannot be accepted in any case unless there has been a careful elimination by clinical, pathologic, and bacteriologic means of all other possible sources. Tompkins,[2] however, says, "Generally speaking, unless there is a clear history to the contrary, obstetricians and gynecologists will not be far wrong in assuming that cases of pneumococcus pelvic disease which they see are the result of ascending infections."

The true nature of the infection was not suspected in either patient until bacteriologic examination of pus was possible, and it is difficult to understand how it could have been otherwise. King[3] emphasizes that the clinical signs of pneumococcus genital tract infection are no different from those caused by other organisms. It should be noted, however, that each of the two patients here reported had the extreme prostration and rapid localization of pus, characteristic, although not diagnostic, of pneumococcus infections.

REFERENCES

(1) *Nuckols, Hugh H., and Hertig, Arthur T.:* AM. J. OBST. & GYNEC. **35:** 782, 1938. (2) *Tompkins, Pendleton:* Ibid. **31:** 70, 1936. (3) *King, James E.:* Ibid. **29:** 341, 1935.

PAUL-HELEN BUILDING
UNIVERSITY HOSPITALS

THE FORMATION OF AN ARTIFICIAL VAGINA WITHOUT OPERATION BY THE FRANK METHOD

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CONGENITAL absence of the vagina is a not infrequent malformation for the correction of which various operative procedures have been devised. In general the methods used are highly technical and require complicated stages of plastic surgery and long periods of hospitalization. Recently Robert T. Frank[1] reported the successful formation of an artificial vagina by a simple nonoperative technique. The principle involved in his method is the production of a hernia of the vestibular mucous membrane into the loose areolar space that lies between the rectum and bladder. The pouch thus formed is of sufficient dimensions and elasticity for coitus and is lined with stratified squamous epithelium almost identical with that of the normal vagina. The method is an office and home procedure without danger, and the end result is free from such esthetic objections as annoying discharges, mutilation of the labia, scarring of the thighs, etc.

We wish to report two cases of successful formation of artificial vagina by the Frank procedure, one of which represents an extension of the method to a patient on whom previous operative procedures had been performed.

CASE 1.—An unmarried white woman, aged 21 years, was admitted to Emory University Hospital July 18, 1938, with the history of never having menstruated. She was told by her family physician that she could not be a "full grown woman" until she had an operation, because she did not have a vagina.

The patient was a well-nourished and well-developed young woman, with essentially feminine secondary sex characteristics. General physical examination was negative except for the pelvis. On exposing the vestibule there was an apparent absence of the vagina. The vaginal orifice was represented by a shallow depression about 1 cm. in depth. Rectal examination revealed a small indefinite cordlike structure in the region normally occupied by the uterus. A small ovary was palpable on the left side; the right ovary was not palpable.

The patient cooperated readily in carrying out the Frank method of treatment. A small glass tube 0.8 cm. in outside diameter was introduced in the center of the slight depression in the hymenal region, and gentle pressure was exerted in a direction backward and inward with the patient in the lithotomy position. She was taught to perform this maneuver and instructed to repeat it three times daily for a period of about a half hour at a time. As the depression increased in depth a longer tube 1.5 cm. in diameter, and finally one 2 cm. in diameter were used.

It was found unnecessary to keep the tube in place during the night with cotton pads and T-binder as advised by Frank. After a period of four months, an artificial vagina was formed which measured 6 cm. in depth, readily admitted two fingers, or a small bivalve Graves' speculum. The canal was lined with soft velvety mucous membrane, sections of which showed it to be normal squamous epithelium. This patient is engaged and expects to be married soon.

CASE 2.—At the Gray Clinic of Grady Hospital, a colored girl of 17 years offered herself for treatment because of absence of the vagina. There was some doubt of the applicability of Frank's method because of the limited intelligence of the patient and because two operative procedures had been performed upon her. The first of these was apparently mere incision into what was thought

to be an imperforate hymen. The last operation was performed at Grady Hospital under a diagnosis of imperforate hymen and hematometrium. Operation disclosed absence of the vagina, and no cervix could be found after exploring the rectovesical space for two inches. Laparotomy then revealed a rudimentary right ovary and cornu and no left adnexa. The supposed hematometrium proved to be a fused pelvic kidney. No attempt was made to line the rectovaginal space with epithelium, and it was allowed to heal. A depression 1 cm. in depth was left in the site of the supposed hymen.

To overcome any difficulty of intelligent cooperation, a device was made which the patient could wear at night and which would exert constant, uniform pressure. This consisted of a short hard glass test tube 2 cm. in diameter with a rubber stopper. It was held in place by means of elastic bands attached to a closed cup-hook in the stopper and to a belt of adhesive tape around the waist (Fig. 1).

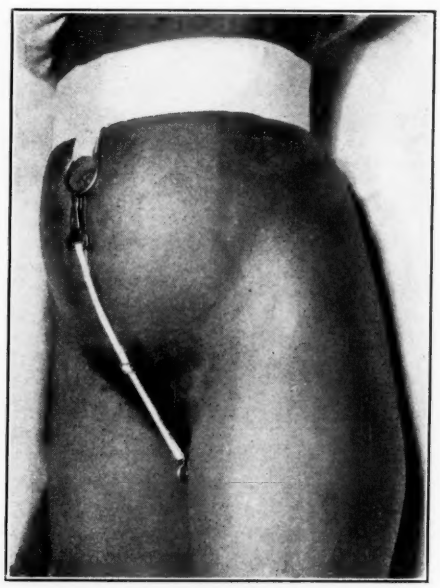

Fig. 1.

The patient was instructed to discontinue the use of the apparatus if any blood, denoting injury to the mucosa, should be found. In addition, for lubrication of the tube, she was given a solution of estrogenic substance in oil to stimulate growth of the epithelium. The test tube was replaced with a longer one as required.

The procedure was rapidly successful, no scarring from the previous operations being met with. At the end of eight weeks a vagina was secured which was 6.5 cm. deep, admitted two fingers, and accommodated a completely opened Graves' virgin speculum for its entire length. The epithelium was intact and was somewhat rugose as in the normal vagina. A pinch biopsy from the depth of this newly made vagina revealed the normal stratified squamous epithelium, typical of the adult vagina.

The patient states that intercourse is perfectly satisfactory to both parties.

REFERENCE

(1) *Frank, R. T.:* Am. J. Obst. & Gynec. **35**: 1053, 1938.

A GRANULOSA CELL TUMOR OF THE OVARY WITH OBSERVATIONS ON RADIOSENSITIVITY*

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IN RECENT gynecologic writings,[1] the subject of granulosa cell tumors of the ovary has received considerable attention. This "newcomer" has been studied clinically, pathologically, and biologically by a number of investigators whose contributions have added to the subject of gynecologic pathology a chapter of lasting interest. Recently, Butterworth[2] submitted valuable histogenic data by his demonstration that tumors, histologically and biologically composed of granulosa cells, could be produced experimentally in mice, by the use of roentgen rays. But the question of radiosensitivity in granulosa cell neoplasms has never been answered satisfactorily. These tumors are comparatively rare and hence, as pointed out by Wolfe and Kaminester,[3] the opportunity for studying their response to radiation is very unusual. For this reason, we believe that the following illustrative report of a case might serve a well-intended purpose.

REPORT OF A CASE

A white woman, aged 49 years, first registered at the Mayo Clinic Nov. 16, 1917, complaining of dizziness. Her family history and personal history were irrelevant. She had had one child in 1897 and two miscarriages shortly thereafter. Menses always had been regular but the flow was becoming scanty. Examination led to a diagnosis of chronic cholecystitis and a menopausal neurosis for both of which conditions a medical regimen was outlined.

On her second admission in September, 1927, at the age of 59 years, the patient stated that, after her apparent menopause in 1924, periods had returned. The bleeding which had occurred with comparative regularity was interrupted by periods of amenorrhea during summer months. Positive physical findings at this time were an enlarged uterus, thought to contain small fibroid tumors.

On Oct. 19, 1927, dilatation and curettage were done with the insertion of radium (1200 mg. hours) designed to hasten the onset of a complete menopause. The pathologic report on the tissue removed was "hypertrophic endometrium."

On her third visit in June, 1930, the patient stated that vaginal bleeding had not occurred from October, 1927, to January, 1930. Since that time, however, there had been irregular spotting with the passage of occasional clots. Two days prior to admission the patient had been seized with severe lower abdominal pain of a cramping nature. The pain had persisted in spite of the administration of morphine. Examination revealed lower abdominal tenderness with rigidity. The uterus was difficult to outline but was enlarged, firm, and tender.

Laparotomy was performed and a hysterectomy with bilateral salpingo-oophorectomy was done because of a hemorrhagic ovarian neoplasm that showed evidence of recent rupture.

The patient was dismissed from the hospital after a satisfactory convalescence. In a follow-up letter, dated July 6, 1937, she reported that "the operation was successful."

Pathologic Examination.—Grossly, the uterus was enlarged in all its dimensions and presented a thick, boggy endometrium which belied the age of the patient. The Fallopian tubes were not remarkable. The left ovary was fibrocystic and

*Submitted for publication, May 9, 1939.

atrophic. The right ovary was replaced by a hemorrhagic tumor that was 8 cm. in diameter. Much of the tumor appeared to be cystic but many solid portions were present. These latter, when freed from blood clots, were composed of a firm, granular substance, grayish brown in color, and resembling liver sausage in consistency. Rupture had occurred and much of the tumor was fragmented. However, careful study revealed the presence of a comparatively smooth capsule. Microscopically, the tumor was a typical, granulosa cell neoplasm of the mixed cylindroid and sarcomatoid patterns (Fig. 1). Vascularity was an outstanding feature. Mitotic figures were few in number and as in most examples of this type of neoplasm were suggestive of a low grade of malignancy.

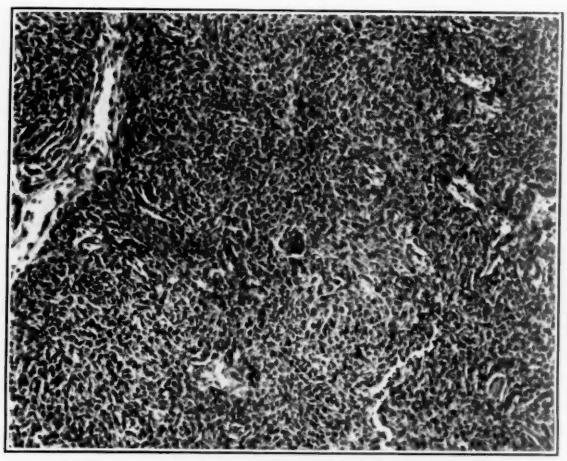

Fig. 1.—Tumor showing the cylindroid pattern of a granulosa cell neoplasm. ×100.

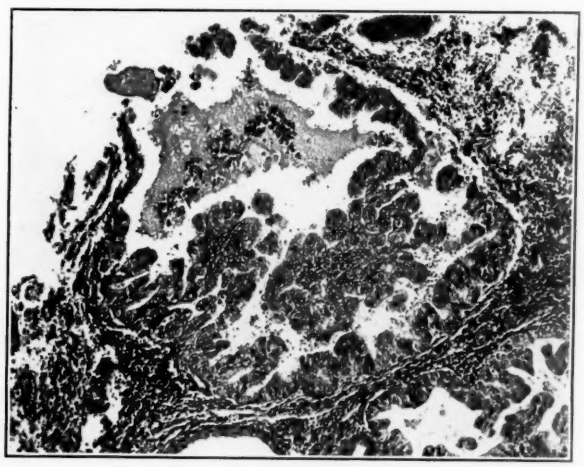

Fig. 2.—Early adenocarcinoma of the uterus associated with a granulosa cell neoplasm.

The endometrium was cystic, reflecting the prolonged action of estrin. Here and there were regions of atypical glandular epithelium forming an adenocarcinoma, Grade 1, in situ (Fig. 2). This latter change was not observed in the tissue removed in 1927 (Fig. 3) which showed the usual picture found in cases of granulosa cell neoplasm.

COMMENT

Probably it will be conceded that the complaint of this patient on her second admission, was due to the presence of a granulosa cell tumor. Recurrent, periodic, postmenopausal bleeding in a woman, aged 59 years, would, today, warrant an exploratory laparotomy. The finding of hypertrophic cystic endometrium would strengthen this conviction even without the evidence suggested by the enlarged uterus which had not been noted at the time of her first admission.

Granting this primary assumption, it would appear from the subsequent history of amenorrhea, two and one-half years in duration, that the small menopausal dose of radium effected a "cure" by causing regression of the tumor. That this effect was not complete, is obvious from the recurrence of symptoms and from the findings at operation. It would indeed be interesting to postulate what additional results would have been obtained had a much larger dose been employed, but further than this we cannot go.

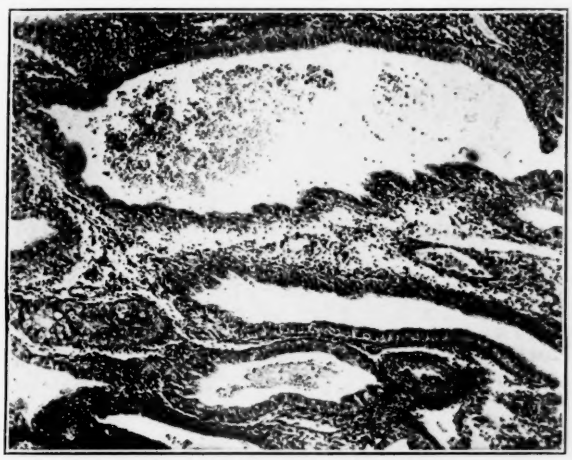

Fig. 3.—The endometrium, showing cystic change.

The finding of an early adenocarcinoma in the endometrium proves to be an additional point of interest and introduces again the question of the carcinogenesis of estrin. We have observed this association in two additional cases of granulosa cell neoplasm, reported recently from this clinic. Finally, the good result obtained in this case emphasizes again the low grade of malignancy commonly demonstrated by granulosa cell tumors.

SUMMARY

An additional case of granulosa cell tumor of the ovary is described. The postmenopausal bleeding produced by this tumor was arrested for a period of thirty-one months by the employment of 1,200 mg. hours of radium. The tumor again made itself manifest after this period and on removal, was found to be associated with an early adenocarcinoma of the endometrium. Recurrence of symptoms was not noted over a period of seven years of postoperative observation.

REFERENCES

(1) *Dockerty, M. B., and MacCarty, W. C.:* Am. J. Obst. & Gynec. **37:** 425, 1939. (2) *Butterworth, J. S.:* Am. J. Cancer **31:** 85, 1937. (3) *Wolfe, S. A., and Kaminester, Sanford:* Am. J. Surg. **31:** 471, 1936.

CARCINOMATOUS TERATOMA (TERATOBLASTOMA) IN A GIRL OF EIGHTEEN*

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THE following case report is presented as an example of this rare condition: H. S., female, aged 16 years, was first seen in March, 1936. She had been under observation for the preceding nine months for recurrent attacks of nausea, vomiting, and abdominal pain. These attacks occurred at irregular intervals, particularly after physical exertion. During this period she also had noticed gradual enlargement of the abdomen. There was an increase in body weight from 128 to 147 pounds.

The diagnosis of gravidity was entertained by her physician, in spite of her repeated assertions that menstruation was always regular and normal. Several Friedmann tests for pregnancy were negative. A diagnosis of ovarian cyst was then made, for treatment of which she was referred to one of us (I. S.).

When seen on March 19, 1936, she was a fairly well-nourished girl, quite apprehensive, somewhat paler than normal but, to all appearances, in good condition. Physical examination was essentially negative. Inspection and palpation showed a large, ovoid intraabdominal tumor, reaching from the symphysis to a level midway between the umbilicus and the diaphragm. The shape and contour of this tumor resembled in every respect a gravid uterus of about seven and one-half months' gestation. The abdominal wall was tense and somewhat tender. The tumor was easily outlined. It was freely movable, cystic in character, and a distinct fluid wave was ascertained. Vaginal examination showed an intact hymen. Rectally, a small cervix was felt high in the pelvis, and the lower pole of the tumor was easily palpable. The diagnosis of a large ovarian cyst was corroborated and operation advised.

Clinical Course.—She disappeared until April, 1938, two years later, at which time she was again referred for consultation by another physician with the following interval history:

Before consenting to an operation, she entered another hospital where she was carefully studied. The diagnosis of ovarian cyst was also made, operation likewise advised and the patient again demurred. Her physician wrote: "Operation had finally been decided upon when she suddenly felt her abdomen become flat again. She experienced no pain, but found that the tumor had suddenly disappeared. Examination at this time (June, 1937) showed the abdomen to be entirely flat with no suspicion of any growth, at least to an extent that might be felt externally. I concluded that she had had a cyst which had ruptured, and advised against operation at this time. No rectal examination was made."

She was again examined by her physician in November, 1937, at which time she was apparently perfectly normal, asymptomatic, and without abdominal enlargement. Rectal examination was not made. In April, 1938, she returned with recurrence of her original symptom. She was advised to enter the Bronx Hospital, which she did on April 16, 1938, and the following was noted:

Hospital Admission (No. 87739).—A young, fairly well-developed girl, not acutely ill, complaining of pain in the abdomen. Menstrual history: Catamenia at thirteen and one-half years, always regular, five-weeks type, flow moderate in amount and lasting about five days. No dysmenorrhea. Last menstrual period was March 16, 1938.

*Presented at a meeting of the New York Academy of Medicine, Section on Obstetrics and Gynecology, December 27, 1938.

Physical Examination.—Palpation of the abdomen revealed a large asymmetrical tumor, extending from the symphysis to somewhat above the umbilicus. It was firm in consistency, irregular in contour and tender on palpation. The tumor was more prominent to the left, but extended for about two inches to the right of the midline. The entire abdominal wall was tense, but there was no rigidity present. Fluid wave was absent. Rectal examination revealed the lower pole of the tumor filling the entire left pelvis. To the right the cervix could be readily felt, and to the right of the cervix there was present a small mass, the exact size and consistency of which could not be definitely outlined.

Laboratory Data.—The urine was negative. Blood examination showed Hb. 80 per cent; red blood count, 4,200,000; white blood count 9,300, of which 74 per cent were polynuclear leucocytes, 20 per cent lymphocytes, and 3 per cent band forms. No other abnormalities were noted.

Operation (I. S.).—April 18, 1938: Bilateral salpingo-oophorectomy under general anesthesia. The abdomen was opened by paramedian incision. There was a small amount of free fluid in the peritoneal cavity. A large cyst presented, extending about half-way to the diaphragm and downward to the pelvis. The cyst was free of adhesions except for a firm band extending from its lower anterior wall to the bladder. This was transected. The tumor was freely movable and attached to the lateral wall of the uterus by a broad thick pedicle. The cyst was isolated by means of wet gauze pads. Owing to its size it was thought advisable to aspirate some of the fluid before removing it. A small trocar was inserted and only a small amount of bloody fluid was obtained, not sufficient in amount to warrant any further attempt. The abdominal incision was therefore enlarged, the cyst delivered, easily removed, and the pedicle stump covered by peritoneum.

The right ovary was palpated, found to be enlarged, freely movable and easily lifted out of the pelvis. It was about the size of an orange, firm in consistency with a fairly well-developed hematoma on its anterior surface. The entire mass was easily removed and the pedicle peritonized.

The uterus was small, freely movable, and appeared to be normal. Inspection and palpation of the entire pelvis showed nothing further of a pathologic nature. Since both tumors were well encapsulated, freely movable and had fairly large pedicles, it was felt that there was no reason for subjecting the patient to hysterectomy. The abdomen was therefore closed and the patient returned to bed in good condition. She made an uneventful recovery, and left the hospital on the twelfth day. She was subsequently referred for high voltage deep x-ray therapy.

Pathologic Report.—Gross description: Pathologic specimen (No. 13852) consisted of tubes and ovaries. The left tube measured 5 cm. in length and showed no gross pathology. Its ovary was enlarged and measured 17 by 15 by 6 cm. and was received partially opened. The surface was smooth and fibrous and exhibited congested veins with no evidence of previous perforation. There was a 4 cm. lobulated projection on the surface of the larger mass. On section of the whole ovary, it was seen to be a large, multilocular, cystic tumor which contained a heterogenous mass of fluid, gelatinous material, yellowish, firm, opaque material, cartilage, bone and an encapsulated mass of reddish brown, friable tissue which occupied about one-third of its substance. The previously described projection on the surface, which seemed to be part of the outer shell, was a loculation which contained hair and sebaceous material, apparently the dermoid area associated with the larger teratomatous cyst. The inner surface of the larger cyst cavities presented several areas of focal sessile papillary proliferation. The third large loculation was filled with solid, friable, opaque and translucent material which was interspersed with numerous small cystic areas and hemorrhage.

The right tube measured about 4 cm. in length and showed no gross pathology. Its ovary measured 4 by 4 by 2 cm. and was received open. It had a multilocular cystic structure. Sebaceous material and hair arising from a nidus on the inner wall occupied the major cyst cavity. The remaining small portion of the ovary contained a hemorrhagic cyst and multiple small serous cysts.

Microscopic.—(1) Material from the larger cystic area of the left ovary shows various types of tissues, frequently in organoid arrangement, including cartilage, bone, skin and sebaceous glands, brain and ependymal structures, myxomatous and fibrous tissue and other glandular elements. (2) Tissue from the solid area of the

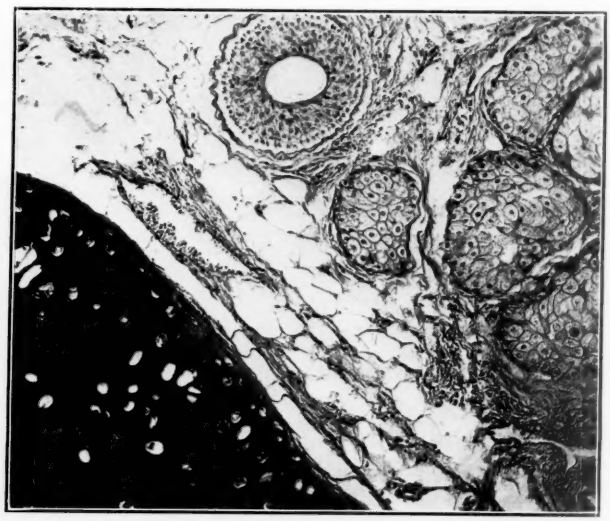

Fig. 1.—Photomicrograph of one area of the teratoblastoma exhibiting cartilage, sebaceous glands, hair follicles, fat and ependymal structures. Other areas showed various types of tissues arising from all three germ layers.

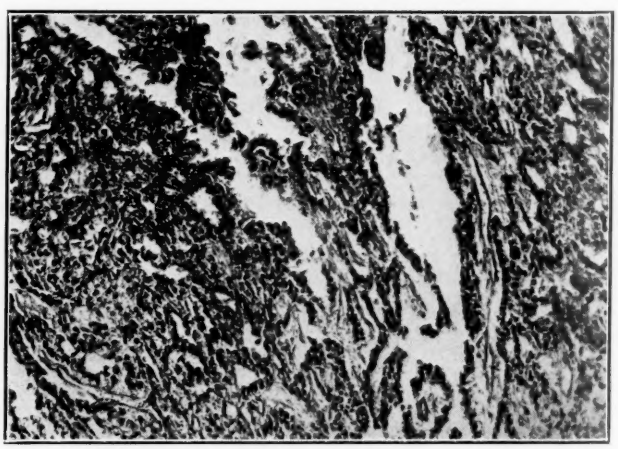

Fig. 2.—A typical section of the anaplastic papillary adenocarcinoma which occupied a large portion of the tumor.

left ovary shows a diffuse growth of anaplastic papillary adenocarcinoma with areas of cystic secretory activity and hemorrhage. (3) Material from the right ovary shows ectodermal elements of hair, skin, and sebaceous glands.

Pathologic Diagnosis.—Left ovary, teratoblastoma with papillary adenocarcinoma; right ovary, dermoid cystoma.

DISCUSSION

The teratoblastoma represented a malignant cystic lesion which, from the clinical course, appeared to have been larger at some previous time with spontaneous rup-

ture or perforation and subsequent diminution in size. So far as could be determined at operation and from the pathologic study, there had been no peritoneal involvement by extension of the malignant process through the capsule or following rupture with dissemination of intracystic material. This fact, in addition to the time element, leads to the assumption that rupture probably occurred from the fluid part of the loculated cystic ovary. It also lends support to the belief that the solid carcinomatous portion of the tumor arose as an area of malignant metaplasia in a previously benign teratoma. Although this is an unusually rare occurrence, it is most probable in this instance because those teratoblastomas which are malignant from their inception usually exhibit early bilateral malignancy and rapid growth. The opposite ovary in this case showed only a benign dermoid cyst and no evidence of carcinomatous extension.

Although hysterectomy was not performed in this young woman, such complete operation with bilateral oophorectomy should be the usual policy in practice where ovarian cancer is found.

The patient has been subjected to high voltage deep roentgen therapy as a prophylactic measure against development of possible disseminated cancer cells. She is now free of clinical evidence of disease almost three years after onset of first symptoms and one year after operation. Her subsequent course is unpredictable, although at this time the outlook is favorable.

Grateful acknowledgment is made to Dr. Joseph Felsen, Director of Laboratories and Research, The Bronx Hospital, for his aid in the preparation of this paper and in the preparation of the photomicrographs with the technical aid of Mr. Thomas E. Ross, photographer to The Bronx Hospital Laboratories.

ABDOMINAL PREGNANCY REQUIRING SECONDARY REMOVAL OF THE PLACENTA

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THE following case history is reported because of its unusual sequela. The authors have not found an identical case reported in the English literature of the last ten years.

The patient was a 38-year-old, gravida iv, para iii, who was referred on March 28, 1939, for care and delivery because of toxemia of pregnancy. She stated that her last menstrual period was July 4, 1938, making her estimated date of confinement, April 11, 1939. For the last month she had had considerable swelling of her feet and ankles and for the past week had backache and some blurring of vision. Her blood pressure had been elevated for the last month. There had been severe abdominal tenderness and pain all during her pregnancy.

Her past medical history was irrelevant. She had had three normal pregnancies, the last one ten years ago.

Physical examination showed an extensive edema. Her face was puffy, hands were swollen, and there was 3+ ankle edema. The abdomen was of normal contour; not easily palpated because of edema of the abdominal wall. Fetal heart was heard in the left lower quadrant.

Vaginal examination revealed a normal-sized pelvis, cervix large, and very edematous. External os could be seen at the introitus and was two fingers dilated. Blood pressure was 175/90. Patient was admitted for treatment of pre-eclampsia.

Urine showed 2+ albumin, blood count, 91 per cent Hg; R.B.C., 4,800,000; W.B.C., 8,600; nonprotein nitrogen, 33; uric acid, 6 mg. per cent.

This patient was given intensive treatment for four days for pre-eclampsia, but did not respond. Blood pressure remained around 175 to 180 systolic, and albumin

remained at 2+. It was decided to induce labor by inserting a bougie. When this was attempted, it was found that the internal os could not be reached because of the markedly elongated cervix, so a small size No. 16 bougie was inserted through the cervix, with only moderate difficulty. The membranes did not rupture.

The bougie was left in place for twenty hours, and during this time the patient complained of severe pains but no uterine contractions could be felt. The abdomen was extremely tender and adequate palpation could not be done. It was decided to do a cesarean section because of severe pre-eclampsia and failure to establish labor by bougie insertion.

A midline incision was made and as the peritoneum was exposed, it was found to be very vascular and thickened. On opening into this, the fetal sac was entered directly and a viable 4 pound 9 ounce female child was extracted. The fetal sac was in the center of the abdominal cavity. The placenta was attached to omentum, ileum, ascending and transverse colon. There was no attachment whatsoever to the uterus or either of the Fallopian tubes. Because of the extensive attachments to the intestines it was decided to leave the placenta in situ. The uterus was the size of a three months' pregnancy. The fetal sac and peritoneum were fused, so they were closed together and without drainage.

The patient's postoperative course was uneventful; only on one occasion did the temperature reach 100.4° F. She was discharged on April 18, 1939, the eighteenth postoperative day, in good condition.

Nothing more was heard from this patient until May 12, 1939, when she returned stating that she had felt well after discharge for one week but gradually began to have loss of weight and appetite. On examination she was weak, pale, and the abdomen was greatly distended and was larger than a term pregnancy. In places this was dull to percussion and in other places tympanitic. Her temperature was 103° F. Blood count showed 60 per cent Hg; R.B.C., 3,000,000; W.B.C., 18,000; 88 per cent neutrophiles. Impression was that there was a large accumulation of pus in the fetal sac.

She was given a 500 c.c. blood transfusion, and then the abdomen was incised in the midline and a large amount of pinkish, gray fluid drained (estimated 3000 c.c.). This was moderately foul in odor; there was also some gas escaped with it. Two large rubber drains were left in the abdominal wound. Bacteriologic studies of the fluid showed no growth on brain broth but *Staphylococcus aureus albus* after four days' growth on blood agar was found.

Following this operation the patient continued to run a temperature elevation and developed a phlebitis of her left leg. A semisolid mass could be palpated in the right upper and middle quadrant. This was considered to be at the site of the placenta and was thought to be another accumulation of pus. Consequently one week later an incision was made over the mass in the right upper quadrant. This was found to be the old placenta which was necrotic at the edges but intact and well encapsulated and was easily shelled out. The peritoneum was thickened and walled off from the peritoneal cavity. There was a direct communication with the lower abscess cavity, consequently the upper abdominal wound was closed and was allowed to drain through the lower incision.

The patient's course following this was uneventful. She was afebrile after the fourth day. She was discharged three weeks after the last operation. There was still a small draining sinus.

Follow-up examination: Aug. 10, 1939. Baby doing very well, weighed 13¼ pounds. Mother had no complaints; no abdominal pain or constipation. Left leg swelled when she was up for a long time.

Physical examination: Abdomen: No masses or tenderness; both incisions well healed. Pelvic: Outlet well supported. Vagina: Healthy mucosa, no discharge. Cervix: Slight central erosion; normal size. Uterus: Normal size, shape, position, and mobility. Adnexa: Normal. Left leg had slight pitting edema about the ankle.

CESAREAN SECTION FOR THE NINTH TIME

DANIEL J. MCSWEENEY, M.D., BOSTON, MASS.

(From the Gynecological and Obstetrical Service of the Boston City Hospital)

IN 1933 when I performed the ninth cesarean section on this patient, who was then 38 years old, she was still desirous of further propagation and apparently well able physically to withstand more pregnancies. Therefore, I have postponed reporting this case until I was reasonably certain she was beyond the age wherein she might surpass her unusual record of multiple cesarean sections.

A careful search through the literature disclosed seven as the highest incidence of cesarean section on one patient as yet reported.[1]

D. C., a white para ix (Hospital Record No. 724592), aged 38 years, entered the Boston City Hospital on Oct. 5, 1933, in mild labor. Her medical history was uneventful. Past surgical history: Cholecystectomy, 1919, appendectomy, 1929. Past obstetric history: (1) Sept. 23, 1912, at New England Sanatorium, Melrose, Massachusetts. Classical cesarean section because of bony dystocia after several hours' test of labor. Normal convalescence. (2) Oct. 27, 1914, at Tewksbury State Hospital, Massachusetts. Classical cesarean section at term. Normal convalescence. (3) April 3, 1916, at Tewksbury State Hospital. Classical cesarean section at term. Normal convalescence. (4) Nov. 9, 1917, at Tewksbury State Hospital. Classical cesarean section at term. Normal convalescence. (5) Oct. 7, 1919, at Tewksbury State Hospital. Classical cesarean section at term. Normal convalescence. (6) Jan. 10, 1922, at Boston City Hospital. Classical cesarean section at term. Normal convalescence. (7) July 21, 1924, at Boston City Hospital. Classical cesarean section at term. Slight wound sepsis. Otherwise normal convalescence. (8) April 17, 1932, at Boston City Hospital. Low cervical cesarean section at eight months because of premature partial separation of the placenta, with death of the fetus. Normal convalescence.

Present Pregnancy.—Last menses began Jan. 5, 1933. Due Oct. 12, 1933. Patient had received no prenatal care (as was her custom). No toxic symptoms. No flow. Baby active. Irregular mild labor pains started about two hours before admission.

Examination.—Patient in mild first stage labor with pains every six to eight minutes lasting twenty-five seconds. Blood pressure 112/68. Urine negative. Uterus at term, vertex floating, left position. Fetal heart in left lower quadrant, rate 138, of good quality. Her pelvis was of the justo minor, generally contracted type with an intercristal diameter of 25 cm., an interspinous of 20 cm., and external conjugate of 17 cm. The symphysis was narrow and the subpubic arch angulated, suggesting a male type of forepelvis. The intertuberous diameter of the outlet was 8 cm. and the posterior sagittal 9 cm. There were four well-healed lower abdominal median and paramedian scars, a firm low right rectus as well as a high right rectus scar. Rectal examination found the cervix partly taken up, one finger dilated, membranes intact, vertex floating.

Operation.—Under gas-oxygen-ether anesthesia a left paramedian scar was resected, exposing a thick mass of dense fibrous scar tissue extending from the subcutaneous plane to the peritoneum. The lower two-thirds of the anterior wall of the uterus were so firmly adherent to the parietal peritoneum that separation was not only impossible but unwise since the uterus could be readily opened with the surrounding peritoneal cavity well walled-off by dense adhesions. A classical type of cesarean section was done and a 7 pound 4 ounce baby extracted without difficulty. Palpation of the uterine wall with the hand in utero after the placenta was extracted disclosed no evidence of any thinning from previous scars. The uterine muscle acted well after intravenous pituitrin and intramuscular ergot. The uterine

wound was closed with two layers of continuous chromic 2 catgut through the muscle and one continuous chromic 2 suture approximating the serosa and adherent parietal peritoneum. Abdominal wall was closed with interrupted silk worm gut in skin. The patient and baby made an uneventful recovery and were discharged well on the sixteenth postoperative day.

This patient, evidently not sated with eleven laparotomies, will enter the hospital in the near future for a bilateral inguinal herniorrhaphy.

I wish to acknowledge the valuable assistance of Miss Helen J. Crowley, of the Social Service Department of the Boston City Hospital, in tracing this patient and compiling the records.

REFERENCE

(1) *Shaw, W. F.:* J. Obst. & Gynaec. Brit. Emp. **28**: 547, 1921.

47 Bay State Road

IMPROVED INSTRUMENT FOR TUBAL INSUFFLATION, SALPINGOGRAPHY, AND AEROUTEROGRAPHY*

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(From the Department of Gynecology, New York Post-Graduate Medical School and Hospital, Columbia University)

THE instrument consists of a straight cannula about 10 inches in length and ⅛ inch in diameter. A solid conical metal obturator surrounds the shaft, and is permanently attached about ¼ inch from the distal end. The width of the base of this obturator is ½ inch, its height about ⅝ inch. At the other end of the cannula there is a regular Luer hub. A one-way stopcock is fastened to a hole drilled on one side of this hub. The stopcock has a projection which permits the attachment of rubber tubing. A metal ring on the hub serves as a convenient finger grip (Fig. 1).

TECHNIQUE

1. *Tubal Insufflation.*—The cervix is exposed and cleansed by wiping with cotton pledgets. The canal, portio, and vaginal mucosa are painted with tincture of iodine. The distal end of the sterilized cannula is introduced directly into the cervical canal. At the proximal end, a 30 c.c. syringe with the piston fully withdrawn is attached to the Luer hub and tightened with a quarter turn of the syringe barrel. The stopcock is opened and a manometer attached to the projection of the stopcock by a short piece of rubber tubing. Inward pressure is exerted on the cannula against the external os to effect firm occlusion of the external os by the obturator. Maintaining the inward pressure, air is slowly injected by pressure on the plunger of the syringe. The interpretation of the test has been outlined in a previous article.[1]

2. *Salpingography.*—The technique is the same as for tubal insufflation except that no manometer is necessary. The stopcock is closed, and 10 c.c. of iodized oil or skiodan acacia mixture are injected. The solution is injected fractionally or completely, and followed by x-ray pictures.

A twenty-four-hour check-up plate is taken afterward.

3. *Aerouterography.*—The preparation is the same as for tubal insufflation, except that a tenaculum is placed on the cervix to hold the cervix and uterus in proper position. Without the traction on the tenaculum, the subsequent x-ray pictures show distortion of the uterine position.

I personally prefer a 100 per cent skiodan solution for this purpose.

The syringe containing 10 c.c. of the solution is attached to the Luer hub and the stopcock closed. Four cubic centimeters of the solution are injected and an x-ray exposure made. The stopcock is then opened allowing the solution to drain

*Instrument supplied by Research Department, Becton, Dickinson & Co.

out of the cannula and the uterine cavity. The cannula may even be withdrawn to allow more complete evacuation of the solution from the uterine cavity. After emptying, another x-ray picture is taken. Another syringe containing air is then attached to the hub of the cannula. Air is injected until a sensation of tension is transmitted through the plunger of the syringe. Maintaining the same pressure, another x-ray picture is taken. This picture shows a contrast delineation of the interior of the uterus.

If desired, the syringe containing the skiodan solution may now be reattached to the cannula and the balance of the solution injected. This is also followed by an x-ray picture. The cannula is then withdrawn. Fifteen minutes later a follow-up x-ray is taken.

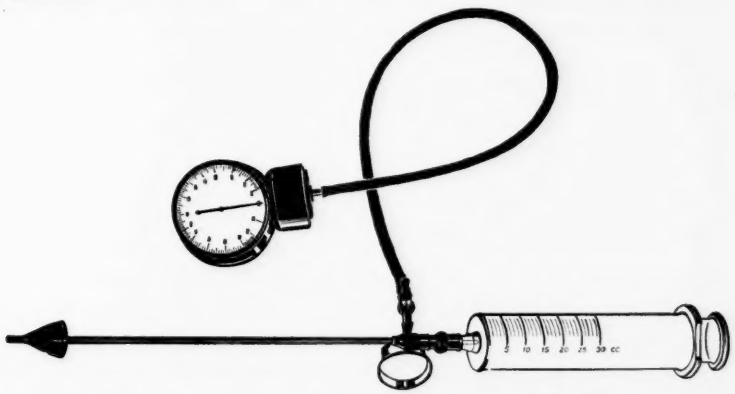

Fig. 1.—Instrument assembled for tubal insufflation.

The addition of the latter part of the procedure, that is, from the injection of the balance of the skiodan onward, permits of a combination of aerouterography and salpingography at the same time.

The findings in patients in whom this technique has been used will be reported in a subsequent communication.

REFERENCE

(1) *Jacoby, A.:* Am. J. Obst. & Gynec. **17**: 871, 1929.

151 West 77th Street

Baker, John R.: The Examination of Semen Specimens, J. Contraception 4: 127, 1939.

The author gives the following suggestions for proper collection of seminal discharge: Condoms used for collection of seminal specimens should be free from spermicidal power as far as possible. The sheet should be free of starch grains, but may be dusted with French chalk or lycopodium. Within at least five minutes after ejaculation the semen should be transferred to a clean glass specimen tube provided with a cork previously soaked in melted paraffin. The tube then is kept at room temperature; body temperature is most undesirable, because spermatozoa use up their store of energy by activity before examination and bacteria multiply. The tube should not be kept in a refrigerator before examination.

Hugo Ehrenfest.

AN UMBILICAL CORD SHIELD

CHARLES W. PAVEY, M.D., COLUMBUS, OHIO

A SUITABLE dressing for the umbilical cord has long been a troublesome nursery problem. The usual practice is to use a small pad of gauze held in place by a roller bandage around the abdomen. The objection to this method in ordinary use is that as often as the baby's diaper is wet the dressing on the cord is wet and, inasmuch as we are particularly interested in promoting the drying of the cord, this constitutes a definite disadvantage that necessitates either frequent changes in the dressing or putting up with a moist cord stump. The method described here has been found to obviate these disadvantages.

A cord protector was devised from a transparent plastic material known as "lucite." This protector consists of a plate of lucite 3¼ inches square. This plate is molded so that it represents a section of the circumference of a cylinder 8 inches in diameter. The center of the plate is then molded so as to create a bulge 1⅜ inches deep. The base of this bulge is of such a diameter as to leave a margin of ½

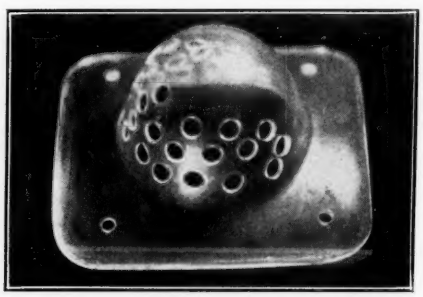

Fig. 1.

inch all around. Numerous perforations, 3/16 inch in diameter, are then put on the upper and lateral aspects of the shield. The part that lies ventral and inferior, that is to say, in the direction of moisture and contamination, remains without perforation.

In using this shield the cord is first tied or clamped, and the shield is then placed over the stump with its curvature conforming to the curvature of the baby's abdomen. It is then fastened in place with adhesive or cellulose tape.

The material from which the shield is constructed softens at 235° F. It is not appreciably affected by acid or alkalies, is practically noninflammable and nonbreakable and, at the same time, is as transparent as glass. It is soluble in acetone.

The advantages of this method are (1) that it provides free ventilation for the cord, thus hastening the drying process, (2) the cord is visible at all times so that its condition can be determined at all times without necessitating the removal of the dressing, and (3) it is protected from the moisture of the diaper.

This device is made by the Ford Ceramic Arts, Columbus, Ohio.

Department of Maternal Welfare

CONDUCTED BY FRED L. ADAIR, M.D., CHICAGO, ILL.

THE SURVIVAL OF THE DIONNE QUINTUPLETS*

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THE Dionne quintuplets are unique because they are the only entire group of quintuplets that have survived for any great period of time. Prior to this event, the longest period of time over which any single quintuplet had survived was fifty days. This record was established by one of a group of quintuplets in 1866, in Lisbon, Portugal. The Lyon quintuplets also survived for a short time. They were born in Kentucky in 1896. The first infant died after four days and by the fourteenth day all had died. It is estimated that quintuplets occur once in every 57 million births.

In the last several centuries, about 60 cases of quintuple births have been reported, all of which are at least fairly well authenticated. However, complete data are lacking. It is known, however, that survival for a few days, hours, or even for a few minutes only, did not occur in any others than those just mentioned.

There are a number of interesting facts which have been garnered about these 60 quintuple births. In 28 of these 60 cases, the age of the mother is known. Quintuplets who do not look alike and are of different sex, are called fraternal. These infants develop from several different eggs. Quintuplets who do look alike and are all of the same sex are called monozygotic. They all come from one egg. The Dionne quintuplets are of this type. Of the 28 mothers of quintuplets whose age is known, the older mothers gave birth to the fraternal sets, and the younger ones to the single-cell type. Only 2 of the 60 births of quintuplets were in mothers having their first baby. The greatest number of quintuplets were born as of the third, fourth, or later pregnancies. From a study of these quintuplets it seems that when the infants were unlike each other, that is, fraternal sets, there was an hereditary tendency in the family for having multiple births, such as twins and triplets. On the other hand, when the sets of quintuplets were like each other, there was no hereditary tendency to multiple births.

In the case of the Dionne quintuplets, there is no history of multiple births, except in distant relatives. From this fact it appears that there is less than the usual chance that there will be twins or other multiple births if there are offspring from the quintuplets.

Besides being of the same sex, the Dionne quintuplets are of the same blood group; are nearly indistinguishable in eye color and pattern, in hair color, and in the amount of skin coloring. The children also share certain rare features, such as syndactylia or webbing of the second and third toes. Throughout the set, the two hands of any one of the children are less like each other than is one of her hands like the corresponding hand of her sister. For example, Marie's right hand and Yvonne's right hand are more alike than are Marie's own right and left hands. This close resemblance which the quintuplets show would not be expected unless all five came from the same egg. Three other of the sets of quintuplets reported appear to have been similarly identical. Thus, the Dionne quintuplets are not unique in this respect; only their survival remains unique in the annals of medicine. This survival, in large measure, has

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been made possible by the scientific developments in pediatrics, as well as by the untiring efforts of a well-trained nursing personnel, in making these discoveries operative.

On May 14, 1914, in Italy, 5 infants, all alive and viable, were born to Rosa Salemi, 40 years old. The first and second lived four days; the third, five days; the fourth, seven days, and the fifth, eight days. It is the opinion of the attending physician that if there had been greater care and assistance on the part of the attendants to whom the children were entrusted, they might have lived as did the Dionne quintuplets.

In the progress of pediatrics, a simple formula for the care of premature infants has been developed, which was followed to the letter from the very beginning in the care of the Dionne quintuplets. This formula, when applied to the care of premature infants in general, and a large percentage of multiple births is in the premature class, may do much to reduce the mortality among these tiny, frail babies. The formula was the one adopted in the care of the Dionne quintuplets including the following:

Premature babies must be kept warm from the moment of birth. They should be kept in surroundings in which the temperature is at least 80° F. They should not be exposed to a temperature lower than this for even an instant. Once a premature baby loses body heat, the strength may be so decreased that the chances of survival may be quickly and completely lost.

The premature infant must be properly fed, and the best food, by all means, is breast milk, if it can possibly be obtained. Of course, vitamins in the form of orange juice and of cod-liver oil, or some similar substance, must be started at the proper time. Every effort must be made to overcome anemia, which is a definite hazard to the premature infant. This can be done by giving egg yolk or some iron preparation.

Premature babies must be protected from infection and therefore must be kept away from any one who is sick. No one should be permitted to handle a premature baby, or even to enter the baby's room without first putting on a clean gown and washing the hands with soap and warm water. Many advocate also the wearing of a face mask by all the attendants.

Oxygen is almost an essential in the care of most premature infants and the method of use will depend on the degree of prematurity and the infant's condition. There can be no doubt that many infants have been saved by the continuous supplying of oxygen. Premature babies develop cyanosis, because very often the lungs are inadequately developed. By supplying oxygen through a face mask, or preferably through a small nasal catheter, or in an oxygen bed if it is available, premature infants have been tided over these cyanotic attacks. In the case of the Dionne quintuplets we used cylinders containing 95 per cent oxygen and 5 per cent carbon dioxide.

Before we obtained oxygen, we had been giving the babies a drop or two of rum when they required stimulation. However, when the oxygen came, we practically stopped giving the rum. Some doctors at that time wrote me to suggest that I should have used brandy, not rum. Well, the fact is that I did not have any brandy. So I had to use what was available.

The eternal vigilance of well-trained nurses overshadows almost every other essential in the care of the premature infant. Premature babies should be under the care of such nurses throughout every minute of the twenty-four hours. During the few minutes when the nurse may be absent from the baby's bedside, an attack of cyanosis, or some other disturbance, may develop, that can prove so damaging that survival is endangered.

The things which are not done for these babies are almost as important as the things which are done. The premature infant is frail, does not stand handling, and must be left undisturbed most of the time. Unnecessary manipulation and over-treatment may be as damaging as neglect.

The Dionne quintuplets are well into their sixth year of life. However, their care after the first year has been no different from that ordinarily supplied

to any well-cared-for infant. It is during the first year and, particularly, the first few weeks that special care is so necessary for premature and tiny infants. Once they have passed through the first year, their development, both physical and mental, goes on in the usual way.

The Dionne quintuplets, 5 tiny girls, were all thrust into the world within a period of an hour. Who was born first and who last is of no significance, except perhaps as a matter of sentimental curiosity. There was too much confusion, too much excitement at the sudden birth of these five babies, in a dark room, only dimly lighted by an oil lamp, to give time for identification or much investigation. Then, too, the mother, whose condition was dangerous and whose very life was at stake, remained the first consideration. As a matter of fact, at first the babies were designated only by letters, A, B, C, D, and E, until names were decided on.

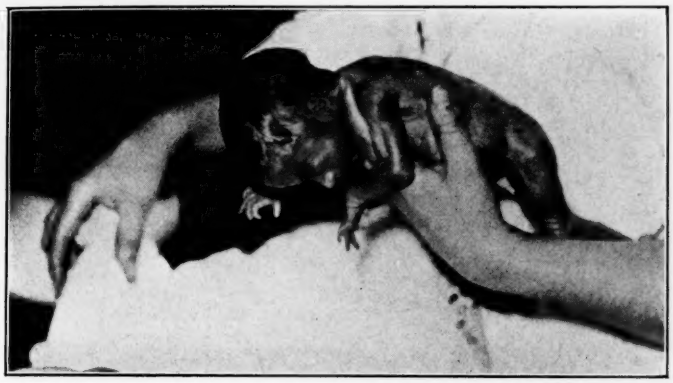

Fig. 1.—Bath time for Marie, aged 2 days.

Of the quintuplets, Marie was the smallest and weakest and Emilie the next smallest. The babies, soon after birth, looked like plucked, wrinkled chickens. Their tiny hands moved in jerky, pathetic movements. As soon as possible after the birth of these babies, some one was sent over to a neighbor's for a basket and returned with an ordinary butcher's meat basket. Heated blankets were placed in the bottom of the basket, and the babies, who right after birth were wrapped in warm coverings made from any old pieces of cloth available, were placed in the basket. Top blankets, which were first warmed, were put over them. These top blankets were changed frequently. In this way, heat was supplied to the infants constantly. Three hours later the babies were taken out of the basket singly, placed on a warm blanket, gently rubbed with warm olive oil, and immediately returned to the basket. All of the early care was given on the nurse's lap. She sat directly before an open oven, which obviated any chance of the infants being chilled. A larger basket was obtained on the second day and hot-water bottles were located and put into the basket. This made it easier to keep the temperature at the proper level. On the third day an incubator arrived from Chicago. This was used to house the three weakest of the infants. There was no room for the others.

After a week, a second incubator arrived, and, finally, there was one for each baby. The temperature in the incubator was kept between 87° and 90° F. at first. As time went on, the temperature was gradually lowered and maintained at 84° F.

As many believe that extra moisture is helpful for premature infants, this was supplied by soaking sponges in hot water. The amount of moisture in the air was kept as closely as possible between 50 and 55 per cent of saturation; that is, 55 per cent of the amount of water that the air would hold.

The slightest change in temperature caused alarming reactions in the babies. A temperature of about 92° F. made their faces flush, and made the infants pant. A temperature of only several degrees below ninety immediately brought on a bluish tinge around the nostrils and caused a rapid increase in breathing.

The babies developed frequent sinking spells. It was necessary for the nurses every minute of the day and night to be constantly on the alert for the development of these spells and to give oxygen at once. This is what I mean by constant watching on the part of the nurses. They did not remove their eyes from these babies for even an instant during the early, critical days.

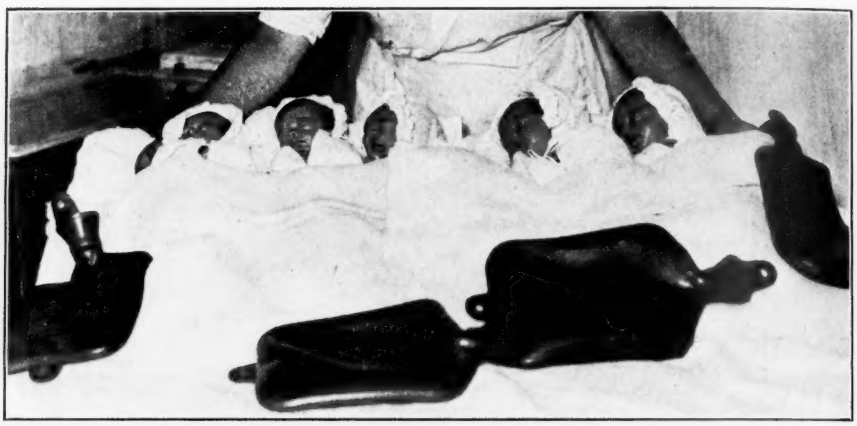

Fig. 2.—The quintuplets at two months. Left to right: Marie, Emelie, Cecile, Annette and Yvonne.

Fig. 3.—Under the sun lamp at 6 months. Left to right: Emelie, Cecile, Marie, Annette, Yvonne.

The babies were kept in the incubators until they reached the weight of six pounds. When they were five pounds in weight the incubators were used as cots, and the extra heating was stopped.

For the first twenty-four hours nothing was given to the babies by mouth but warm water every two hours. After this twenty-four-hour period, feedings were started. The milk was given to them from a medicine dropper. By the fourth day the infants were receiving breast milk boiled, full strength, and from that time on until the fifth month, the only milk the babies received was breast milk.

On the fourth day the babies were able to take their nourishment from a Breck feeder, which method was continued until the babies grew strong enough to take their feedings from a bottle, at six weeks of age. The two-hour feeding interval was gradually increased to two and a half and then to three hours, until at ten months of age, the babies were fed four times a day.

For the first three and a half months the nursery for the quintuplets was included in the limited space provided by a house of three rooms and a summer kitchen on the ground floor, and three bedrooms upstairs. In these rooms dwelt the family, consisting of the father, the mother, five children, two maids, one janitor, two nurses, and five premature babies. The equipment available for caring for the quintuplets was limited. Yet, the constant vigilance of the nurses and the application of simple rules, together with the inherited vitality, permitted these babies to live.

The Dionne quintuplets, it is estimated, were born at about the seventh month of pregnancy. The combined weight at the time of birth as shown by weighing the infants on an ordinary household scale, was about 13 pounds, 6 ounces. After about a week, when weighed on an accurate scale, the combined weight of the five babies was less than ten pounds. The two heaviest weighed a little over two pounds each. Cecile, Emilie, and Marie weighed less than two pounds. Marie, the smallest, weighed only one pound, eight and one-half ounces.

After the confusion of the first week passed, the organized plan for the care of the quintuplets began to function more smoothly, and the opportunity presented itself to do other less necessary but still important things. The doors and windows were screened to shut out flies and mosquitoes. The babies' room was carefully gone over and every possible measure of aseptic technique, such as hand washing, proper waste disposal, and suitable ventilation, was provided. The rest of the children of the family were removed to other quarters, as several of them had developed bronchitis, which it was thought would be dangerous to the babies. No one entered the small nursery but the nurses, the doctor, and occasionally, the parents. Every one without exception, who crossed the threshold, wore a mask over the face, because we wished to do everything possible to help protect the quintuplets. They were kept away from as many sources of infection as was humanly possible. All hands touching them at any time were well washed with soap and warm water. Every care was taken to prevent exposure of these babies to infection, and the results seem to have justified the means.

The quintuplets were given the only natural, correct diet on which they could have a chance of surviving, breast milk. If mother's milk had not been secured in sufficient quantities at the right time, I feel certain the quintuplets would not have lived.

In spite of their prematurity, these five girls have progressed rapidly in physical development, so that now they have reached or exceeded normal levels for height and weight. Their general health and development have been normal, and there is no evidence of any physical or mental abnormality or subnormality as a result of their premature birth.

They have had setbacks, it is true. In the early fall of 1934, every baby in turn suffered from a severe type of intestinal infection, which developed suddenly. Improper sterilization of the diapers was considered a possible source for spreading the infection, but where the infection came from originally has not been determined. In recent years outbreaks of this sort in newborn nurseries all over the United States and Canada have not been unusual, nor has their true cause been determined as yet.

Anemia, which was present in the babies before this infection, became more marked after it. Therefore, small doses of ferrous chloride were given to the babies three times a day, in their feedings, and these were kept up until the infants were over one year old. Orange juice, cod-liver oil, cereals, vegetables, and other necessary foods were added to the diet of the infants as their development warranted.

Carefully observed regularity has been the essential principle in the later general care of these children. If there are any items in the care of these babies which deserve stressing, they are these: First, no fancy or unusual equipment

was necessary. Second, there was a steadfast refusal to indulge in experiments of any kind in their care, although temptations to do so were great. Third, no unnecessary handling was permitted at any time. Fourth, continued viligance, day and night, every minute, on the part of the nurses, assured that every emergency would be met properly and that the babies would be given at the right moment those things which they needed to tide them over a critical period.

Application of a similar simple formula in the care of any premature baby should give the baby the maximum chance of living, and should lead to a reduction in the infant death rates.

The Quintuplet Guardianship Act passed by the Ontario Government, placed the Dionne quintuplets under control of the Crown and appointed a Guardianship for them until they reach the age of eighteen. The guardians are, first, the father, then Judge Valin, a retired jurist of North Bay, the Official Guardian of Ontario, and myself. The guardians meet once a month. They have full control of all business affairs and other matters pertaining to the children's estate. They make contracts, pay expenses, and in general, carry on the duties associated with the children's care and welfare. That this plan is successful is attested to by the health and happiness of the children. All matters concerning the health and well-being of the children are left to me.

Modern pediatrics teaches us that if the premature baby is to have his chance for life, these are the things he needs:

1. Constant maintenance of body heat.
2. Provision of breast milk without meddlesome experimentation with other foods.
3. Giving of oxygen at every critical moment during the twenty-four hours.
4. Avoidance of infection.
5. Vigilant nursing by well-trained nurses, who do not relax in their care for even a moment, working under the constant direction of the doctor.
6. Knowing what not to do, which is at least as important as knowing what to do.

These are the things which undoubtedly made it possible for the Dionne quintuplets to be the first quintuplets to survive, and this without costly or complicated equipment. But it did require eternal vigilance without a moment's cessation, by well-trained personnel.

Past failures with quintuplets, in my opinion, may be charged to the momentary cessation of vigilance in any one of these essentials. With the valuable advice of so many fine experts at my disposal, the task of caring for the five girls has been made easier.

I would like to mention the numerous men of both Canada and the United States, who have helped me with their advice and their services from time to time. However, the list would be too long to include here. But, I cannot let this opportunity pass without telling you about the part played by Dr. Herman N. Bundesen, President of the Board of Health of the City of Chicago. As soon as he heard the news of the quintuplets' birth, he called me on the long-distance telephone and gave me valuable advice. He also dispatched to us by aeroplane our first supply of mother's milk. I also want to mention Dr. Alan Brown, one of Canada's outstanding pediatricians. He arranged for a continuous supply of mother's milk for us from Toronto, and he has come to our assistance many times when we have needed him.

I have also had the services of my brother, Dr. William Dafoe, at my disposal; I have used them many times.

It is my hope that our experience with the Dionne quintuplets will be of some service in guiding others who are confronted with similar problems in the care of premature babies.

Our experiences with the quintuplets lead us to believe that, when such procedures as we adopted are followed, there may be a material reduction in deaths, especially of premature babies, whose death rate is one of the major problems confronting us in reducing infant mortality.

Society Transactions

OBSTETRICAL SOCIETY OF PHILADELPHIA

MEETING OF MAY 4, 1939

Report of a Case of Calareous Degeneration in Uterine Fibromyoma. Dr. H. J. Sangmeister.

Acute Inversion of the Puerperal Uterus. Drs. W. B. Harer and J. A. Sharkey. (J. A. M. A. In press.)

Analysis of 1,000 Consecutive Stillbirths in the Philadelphia Area. Drs. Arthur First, John Sharkey and Thaddeus L. Montgomery. (Report of a special committee.) (For original article see "The Child," published by the Federal Children's Bureau, September, 1939.)

Hildebrandt: Significance of Achylic Chloranemia (Essential Hypochromic Anemia) in Gynecology, Arch. f. Gynäk. **165:** 164, 1937.

Knowledge about achylic chloranemia is not sufficiently disseminated and the disorder does not receive the attention it deserves. The varying interpretation of the leading symptoms is the reason why so many different terms have been applied to the disorder which is much more frequent in women than in men. The patients frequently complain of fatigue, lack of energy, palpitation, tinnitus aurium, attacks of fainting, painfulness of the bones, loss of weight and gastrointestinal disturbances, such as lack of appetite, flatulence, constipation or, more frequently, diarrhea.

The objective symptoms are similar to those of pernicious anemia: there are changes in the lingual mucosa, trophic disturbances in the appendages of the skin, particularly of the nails, and rhagades. The skin is often pale white. The chief symptom of achylic chloranemia is a disturbance in the secretion of the gastric juice. Examination of the blood is of great importance for the diagnosis of the disease.

The author emphasizes that menstrual anomalies and genital hemorrhages are likely to appear during this type of anemia. Schulten, on the basis of 50 cases, estimated the incidence of severe menstrual hemorrhages in achylic chloranemia at approximately 75 per cent. Iron therapy is the method of choice, reduced iron, 1 gm. three times daily, and to intensify the action of the iron, hydrochloric acid is added. This therapy must be continued until a considerable improvement is noticeable in the blood status. The menstrual disturbances or genital hemorrhages that may exist improve simultaneously with the blood status.

J. P. GREENHILL.

Department of Reviews and Abstracts

CONDUCTED BY HUGO EHRENFEST, M.D.

Selected Abstracts

Carcinoma

Imamura, S.: Heredity in Patients With Carcinoma of the Uterus, Jap. J. Obst. & Gynec. **21**: 127, 1938.

Imamura investigated the heredity of all the patients who entered the Kyoto Imperial University Hospital during the years 1923 to 1934 with carcinoma of the uterus. He found a family history of cancer in 9.4 per cent of all the patients who had tumors of the uterus. Of the ancestors who had carcinoma, it was the mother in 33.7 per cent and the father in 24.3 per cent. Next in order were aunts, sisters, brothers, grandfathers, grandmothers, and uncles. The final analysis proved that the maternal relatives supplied 58.5 per cent of the familial cases of carcinoma, whereas the paternal relatives furnished only 41.5 per cent. The organ most involved in the relatives are in the order of frequency: the stomach (47.4 per cent), uterus (33.7 per cent), esophagus, liver, and intestines.

The author's incidence of family carcinoma approximates the figures reported by Schroeder (8.2 per cent), Gusserow (10 per cent), and others. The author found that a woman with carcinoma of the uterus transmits the tendency to cancer to her descendants, and the latter if females tended to have cancer in the uterus more often than in other organs.

J. P. GREENHILL.

Béclère, C.: The Frequency of Cancer of the Body of the Uterus After the Menopause, Compt. rend. Soc. Franc. de Gynec. **8**: 99, 1938.

There exist two opinions concerning the frequency of carcinoma of the uterine body after the menopause. One is that when a woman begins to bleed after the change of life the chances are nine out of ten that she has a cancer of the body of the uterus. It is therefore useless to attempt to make a more exact diagnosis. The uterus should be removed. The second opinion is that only about 50 per cent of women who bleed after the menopause have cancer. To this opinion the author subscribes and he has collected from the literature reports of 1,203 cases of bleeding after the menopause. Cancer was present in only 40 per cent of these collected cases. The incidence of cancer in the individual series varied from 33 to 67 per cent. These statistics provide a good reason for not performing a hysterectomy routinely when women bleed after the menopause. In all cases a biopsy should first be performed and if cancer is found then and then only should the uterus be removed.

J. P. GREENHILL.

Olch, Isaac Y.: Menopausal Age in Women With Cancer of the Breast, Am. J. Cancer **30**: 563, 1937.

Combination of available statistics seems to show that about 71.7 per cent of women pass through the menopause between the ages of 40 and 50. If one notes the menopausal age of older women with mammary cancer, one is immediately struck with the greatly increased percentage who have delayed menopause.

Investigating the age of menopause in 342 women over fifty when first seen for a breast cancer, Olch found that among them were 54.7 per cent who either were still menstruating or had passed through the menopause after the age

of fifty. That is, as compared with normal women in this group almost five times as many had a delayed menopause. He refers to recent reports of delayed menopause in cases of adenocarcinoma of the uterus, suggesting the advisability of artificial x-ray termination of unduly prolonged ovarian activity. Thus Olch arrives at the conclusion that an artificial menopause at some arbitrary age between 48 or 50 might possibly be of prophylactic value against the formation of a mammary cancer.

HUGO EHRENFEST.

Stevenson, Charles Summers and Scipiades, Elemer, Jr.: Non-Invasive Potential "Carcinoma" of the Cervix, Surg. Gynec. Obst. **66**: 822, 1938.

Cancer is the second most frequent cause of death in the western world; cancer of the uterus is responsible for one-third of the cancer deaths in women; 90 per cent of uterine cancer arises in the portio of the cervix and is thus easily accessible for examination and study. The most favorable statistics from the treatment of cancer when it is limited to the portio of the cervix show a 52 per cent cure, while not more than 20 per cent of all cervical cancers have a five-year cure. Schottlaender and Kermauner (1912) and Schiller (1927) have described and called attention to a form of superficial non-invasive cervical "carcinoma." Schiller considers and treats it as definite carcinoma. The authors present 18 cases for which one of them (C. S. S.) has proposed the name "non-invasive potential 'carcinoma' of the cervix." In 1 patient (Case 2) the "carcinoma" remained non-invasive for eight years and one month, following which it developed into a clinical carcinoma and finally caused the death of the patient. A second patient (Case 13) died of pernicious anemia three years after the first biopsy examination revealed a non-invasive potential "carcinoma." Serial sections of this cervix revealed that invasion had taken place shortly before death.

WM. C. HENSKE.

Emge, Ludwig A.: The Significance of Estrogenic Hormones in Carcinogenesis, West. J. Surg. **47**: 107, 1939.

Certain recent studies of mammary cancer in mice suggest that estrogenic hormones may have a more important part in the mechanism of carcinogenesis than heretofore shown for other hormones. In the light of modern research, it is no longer tenable to speak of cancer as a single disease, or as having a single cause. The causes vary with the types of cancer, the organs, and the species.

Experiments made by Emge with various doses of estrogenic hormones administered exogenously over different periods of time yielded various degrees of hyperplasia in breast tissue, mammary adenofibromas, and in the linings and glands of the genital tract. Doses of inordinate size resulted in cystic mastoplasias and genital metaplasias, but even with huge superstimulation the resultant hyperplasia of any of these tissues never approached a truly malignant state.

The author concludes that on the basis of experimental evidence, the relation of estrogenic hormones to cancer is secondary to, and strictly limited by, hereditary factors. It is entirely unlikely that the estrogenic hormones have a broader carcinogenic significance. However, as a matter of caution, it is wise to watch for unusual occurrences in man because of the comparatively short time since the introduction of estrogenic therapy.

HUGO EHRENFEST.

Sorba, M.: Syphilis and Cancer of the Cervix, Monatschr. f. Geburtsh. u. Gynäk. **109**: 73, 1939.

In the differential diagnosis between syphilis and cancer of the cervix, errors are made because a biopsy is not done and syphilis is not thought of. Sorba's statistics revealed that among 262 cases of cancer of the uterine cervix, syphilis

was present in between 14 and 15 per cent. The frequency of syphilis in the other patients in his clinic was only 1.6 per cent. The author believes that syphilis plays a rôle in the etiology of carcinoma of the cervix. However, syphilis only gives the impetus for the development of cancer. The prophylaxis and treatment of syphilis in women will reduce the number of cases of cancer of the cervix.

J. P. GREENHILL.

Belonoschkin, B.: The Rare Occurrence of Adenocarcinoma of the Cervix During Thyrotoxicosis, Klin. Wchnschr. **27**: 1117, 1938.

The author describes the occurrence of an adenocarcinoma of the cervix in a patient suffering from an acute thyrotoxicosis and comments on the rarity of the combination of these two conditions. The thyrotoxicosis contraindicated surgical intervention, and the patient was given combined radium and roentgen irradiation. A fatal outcome resulted from the pyometra and pyosalpinx which followed. The endometrium which had been recently subjected to this irradiation showed marked inflammatory reaction to the irradiation plus many areas of local necrosis. Some areas showed a complete disappearance of the endometrium. Irradiation thus produced complete endometrial atrophy in a comparatively short space of time. The author cites two additional cases that bear out this observation. The author then attempts to show that thyrotoxicosis prevents follicle hormone formation. Since it is this latter which stimulates malignancy by virtue of its carcinogenic properties, its inhibition by hyperthyroidism results in the rare occurrence of simultaneous thyrotoxicosis and genital malignancy.

RALPH A. REIS.

Schiller, Walter: Early Diagnosis of Cancer of the Cervix Uteri, New England J. Med. **218**: 878, 1938.

The human cervix uteri consists of two entities, the external os and the internal os. By naked-eye inspection the external os is defined as that part between the narrow cervical canal and the surface of the vaginal portion. This is called the anatomic external os. By microscopic examination, the external os is defined as that point where the nonhornified stratified squamous epithelium of the portio meets the high columnar mucinous epithelium, containing many glands, which lines the cervical canal. This the author calls the histologic external os.

When the cervical mucous membrane is not limited to the cervical canal but extends out to cover, in varying degrees, the area about the external os, there is an abnormality which occurs in a certain disturbance of fetal development. Only a small percentage of all women retain this congenital eversion throughout life.

On the other hand, in hypoplastic individuals with genital infantilism, it is found that the squamous epithelium of the external os ascends into the lower part of the cervical canal, occasionally up to half or even three-fourths of its length. This variation is of great practical importance in certain cases of carcinoma. Since carcinoma of the squamous epithelium generally begins next to the high columnar epithelium, the greater part of the initial carcinoma in such cases may develop by carcinomatous transformation of the squamous epithelium which lines the cervical canal.

The most frequent lesion of the cervix is erosion. By this term is meant a defect only in the epithelium as compared with an ulcer, in which the underlying connective tissue is also defective.

The precipitating cause of most of the erosions is the macerating influence of a discharge. This accounts for the fact that in nearly all cases of erosion a final and permanent healing can only be achieved when the causal cervicitis has been cured. In the healing of an erosion at the histologic os, an activity of both types of epithelium is observed: the columnar from the cervical canal and the squamous from the periphery are trying to establish themselves on the free and naked surface of the erosion. The columnar epithelium, which consists of one row

of cells only, grows more quickly and succeeds in covering most of the field of the erosion. This is called the first stage of healing. Later on, the slower-growing squamous epithelium begins to creep over or under the columnar layer. This is the second stage of healing.

The therapy of the erosion therefore falls into three stages: first, the healing of the discharge; second, the combating of the inflammation; and third, the stimulating of the potential activity of the neighboring squamous epithelium by substances that support epithelial growth, such as scarlet red.

The most important lesion of the cervix is squamous cell carcinoma, which accounts for about 90 per cent of the uterine carcinomas, whereas the type arising from the glandular epithelium of the cervix represents roughly 2 per cent. The balance, 8 per cent, is accounted for by carcinoma of the endometrium.

A biologic difference between normal and carcinomatous epithelium can be utilized to establish a clinically visible difference in the two epitheliums. The normal epithelium of the cervix contains, in the superficial cell layers, large quantities of granular glycogen, which is produced and stored by the cells. Carcinomatous epithelium loses the potency to produce as well as to store glycogen and is therefore free from this substance. To differentiate the glycogen-containing and glycogen-free areas, the cervix is brought in contact with a dilute aqueous solution of iodine. The best solution has been found to be one containing 1 gm. of iodine, 2 gm. of potassium iodide and 300 c.c. of water. This solution stains the normal, glycogen-containing cervical epithelium, a dark brown, whereas carcinomatous epithelium remains pale. There are several other pathologic changes which also prevent the production and storage of glycogen. Since only a biopsy of the surface epithelium is necessary, there is no need for an exploratory excision: scraping the surface epithelium with a sharp curette is sufficient. The diagnosis can and should be made before the phase of downgrowth.

J. P. GREENHILL.

Geisendorf, W.: Some Observations on the Colposcope, Bull. Soc. d'obst. et de gynéc. **28**: 128, 1939.

Geisendorf was skeptical of the value of the colposcope until he went to visit Hinselmann. After studying the colposcope for a month he became convinced that this instrument not only permits better observations of cervicitis, vaginitis, leucorrhea, and traumatic lesions but that above all it is the only means of detecting early cancer of the cervix. Cancer of the cervix can develop only in abnormal or atypical epithelium which can be recognized with the colposcope. This instrument should not be used only in women suspected of having cancer but employed routinely in all women. The Schiller test is a valuable adjunct to colposcopy but it alone cannot reveal cancer.

In the discussion of this paper Reeb mentioned the fact that Hinselmann found cancer in 45 of 18,000 women examined by means of the colposcope. This is an incidence of 0.25 per cent. Wispe found cancer in 0.12 per cent of 4,000 women examined with the colposcope. On the other hand, V. Mickulicz examined women only by clinical means without the aid of a colposcope and in a series of 2,597 women who had absolutely no subjective symptoms, he found three cancers in the biopsies removed in the suspicious cases. Hence, his incidence of cancer was 0.115 per cent. Reeb, therefore, concludes that there is practically no difference in examining women with and without the colposcope as regards the detection of early carcinoma of the cervix. However, the clinical examination must be thorough.

J. P. GREENHILL.

Wolner, Anthony: The Early Diagnosis of Cervical Carcinoma, Surg. Gynec. Obst. **68**: 147, 1939.

The study is based on 59 cases in which a routine removal of the cervical mucosa was done for purposes of a systematic histologic investigation. Although none of the cases revealed symptoms or clinical findings which indicated

malignancy, in two patients definite cervical carcinoma was found. In both patients a simple excision of the endocervix apparently effected a cure. The experiences justify the following recommendations: (1) No diagnostic curettage should be considered complete without removal and histologic examination of the cervical mucosa. After dilatation and curettage, the Hyams conization offers the simplest and safest way to accomplish this purpose. (2) Every woman past her thirtieth year should be considered a potential candidate for cervical carcinoma. It is advisable for patients in this age group to have at least one routine tissue examination of the lower half of the cervical mucosa. The only contraindication for this procedure is inflammation or tenderness in the adnexa.

Gynecologists who adopt these two recommendations, may be rewarded by the gratifying experience of recognizing and curing an occasional patient with incipient cervical carcinoma.

WM. C. HENSKE.

Aschheim, S.: Difficulties in the Histologic Diagnosis of Benign and Malignant Transformations of the Uterine Endometrium, Rev. franç. de gynéc. et d'obst. 33: 471, 1938.

Not infrequently histologic sections of endometrium present difficulties in determining whether or not the tissue is benign or malignant. Aschheim reviews some cases reported in the literature where a diagnosis of cancer was made and an operation performed because nodules of squamous epithelium were found in the uterine endometrium. He himself has encountered this condition nine times. Even today there is very little in the literature concerning this condition.

The squamous cells, which are found in the uterine endometrium, differ from squamous cell carcinoma in that nearly all the cells are of equal size, they are compact or separated only by a tiny space, but they have no intercellular bridges of tissue between them. Their nuclei are round or oval, they stain faintly with hematoxylin, there is no atypia, there are no giant cells, and mitoses are rare. In the author's experience there was often an edematous and leucocytic infiltration in the stroma.

The author believes that the squamous cells are the result of an irritation of the columnar cells of the endometrium. Such an irritation may be an inflammation combined with irritation due to estrogenic hormone. It is well known that squamous epithelium has been found in the uterine endometrium in the presence of gonococcal infections and also that in the rat and mouse, injections of estrogenic substance will bring about a transformation of uterine endometrium into squamous epithelium. In the treatment of these cases the decision must rest on the clinical symptoms and not only on the histologic appearances. In young women therefore therapy should be conservative and should consist of repeated curettements. Cure will follow in many cases. On the other hand, in older women if hemorrhage recurs, it is best to perform a hysterectomy.

J. P. GREENHILL.

Filkel, R. K.: The Polarigraphic Study of the Serum of Women With Carcinoma of the Genitalia, Zentralbl. f. Gynäk. 63: 647, 1939.

A new serologic test of carcinoma is described. It consists of a polarigraphic study of the serum. In a series of 176 cases of carcinoma, the diagnosis was correctly made in 92.6 per cent, and among 107 cases of recurrence of cancer, the incidence of correct diagnosis was 88.9 per cent. Early carcinoma could be detected in 87 per cent of the cases. However, the cancer reaction is not specific, because a positive test may be obtained in cases of pelvic inflammation. In spite of this the test proved helpful in cases of recurrence and in doubtful cases.

J. P. GREENHILL.

Leip and Otto: Cervical Carcinoma Which Arose on 12 Year Old Leukoplakia, Zentralbl. f. Gynäk. **61:** 242, 1937.

This patient was carefully observed for twelve years, during which time she had a leucoplakia of the cervix. At the end of this time carcinoma developed on the site of the leucoplakia. This case and those reported by others support Hinselmann's contention that the average latent period for development of a carcinoma from the matrix zone is between ten and fifteen years. Hinselmann's advice to remove and examine such matrix zones should be followed.

J. P. GREENHILL.

Holtermann: Abnormally Slow Growing Carcinoma of the Cervix, Zentralbl. f. Gynäk. **61:** 564, 1937.

The writer reports the case of a 41-year-old woman who had a carcinoma of the cervix which remained in an operable condition for twenty-one months after the first appearance of clinical symptoms and fifteen months after a histologic diagnosis was made. The patient was given radium treatment seventeen months after histologic diagnosis was made, and the uterus was then removed. The patient was alive and well more than five years after treatment was begun. The author reports two similar cases. All three patients were relatively young (34, 41, and 44), all did not have treatment for many months after the diagnosis was made (10, 15, and 15 months), and all were alive and free from recurrence since combined radium and operative therapy. Despite these exceptions, all patients with a diagnosis of carcinoma of the cervix should be treated without delay.

J. P. GREENHILL.

Todd, T. F.: Two Cases of Carcinoma of the Cervix in Procidentia Uteri, Proc. Roy. Soc. Med. **30:** 1343, 1937.

The rarity of cervical carcinoma associated with complete prolapse of the uterus is one of the most striking contrary findings to the commonly accepted theory that chronic irritation is an important etiologic factor in the genesis of cancer. Procidentia is common, yet there are less than 40 cases of superimposed cervical cancer on record, to which the writer adds two new observations. The first case concerns a 41-year-old para vi, seen less than a year after her last full-term delivery. A vaginal panhysterectomy was done, followed by local radium application and deep x-ray therapy. She died about eleven months later with a large abdominal mass.

The second case occurred in a para ii, aged 62 years. She had the prolapse for twelve years and off and on wore a pessary. She received radium and x-rays. The local lesion disappeared within a month, and there has been no recurrence so far. (No dates are given.)

HUGO EHRENFEST.

Basden, M.: Carcinoma of the Vagina Complicating a Complete Procidentia, Proc. Roy. Soc. Med. **30:** 1483, 1937.

By means of a vaginal hysterectomy the prolapsed uterus and vagina were removed. There was a carcinomatous ulceration on either side of the vagina. Many years ago patient had worn a ring pessary but not for the past seventeen years. She made a good recovery but refused a suggested removal of the inguinal glands. At the Marie Curie Hospital among about 1,600 cases of cancer of the female genitalia, there were several cases of complete prolapse associated with carcinoma of the fundus but only two with cervical cancer. (Cancers with slighter degrees of procidentia are not included in this figure.) It is interesting to note that in one of the two cervical cancers with complete prolapse, radium application cured not only the cancer but also the prolapse by the resulting contraction.

In discussing this report, Clemmey mentions that while working in East Africa, he had seen two instances of cervical cancer with complete procidentia in native women.

HUGO EHRENFEST.

Oyarzun, Romeo Cadiz: Primary Cancer of the Vagina, Bol. Soc. chilena de obst. v ginec. **11:** 7, 1937.

The author states that primary cancer of the vagina occurs in only 2.2 per cent of all genital cancers. Four cases are reported. The author prefers surgical treatment in Grades 1 and 2 types of cancer of the vagina.

MARIO A. CASTALLO.

Pund, Edgar, and Greenblatt, Robert: Granuloma Venereum of Cervix Uteri (Granuloma Inguinale) Simulating Carcinoma, J. A. M. A. **108:** 1401, 1937.

A heretofore unrecognized entity, granuloma venereum of the cervix, clinically simulates carcinoma of the cervix. Since the involvement by the Donovan body occurs elsewhere than in the groin and on the external genitalia, the name of granuloma venereum is preferable. It is characterized clinically by a tuft of reddish meaty tissue, raised above the surface, clean in appearance, velvety soft and resilient to palpation, and it does not bleed readily to touch. Histopathologically, the essential features are the exuberant granulation tissue reaction in which the pathognomonic cell is found. This cell is a large mononuclear cell with intracytoplasmic spaces in which are dispersed the so-called Donovan bodies. The affinity of the intracystic bodies for silver salts facilitates the recognition of the characteristic cell. With silver these bodies are stained black to brown and have a safety pin appearance because of their elongated ovoid outline and intense bipolar staining reaction.

GROVER LIESE.

Keller, R., and Meyer, P.: Some Considerations of Cancer of the Body of the Uterus, Rev. franç. de gynéc. et d'obst. **34:** 149, 1939.

The authors observed 82 cases of cancer of the body of the uterus in which the diagnosis was made by means of a histologic examination of tissue obtained by curettement. Of the 82 patients, 55 were subjected to operation, 24 had radiation therapy and three were not treated. The postoperative mortality for the abdominal operation was 17.8 per cent and for the vaginal operation 3.8 per cent. The total incidence of cure for all the methods of treatment was 53.4 per cent. The patients treated by radiation alone of whom there were only 14 inoperable cases, yielded a cure rate of 35.7 per cent.

The treatment of choice in operable cases of carcinoma of the body of the uterus is operation. If the patient is in good condition, the operation should consist of total abdominal hysterectomy with removal of the adnexa. In patients with low resistance and in very old women, a vaginal hysterectomy should be performed. Inoperable cases should be treated by radiation therapy.

J. P. GREENHILL.

Handley, R. S., and Howkins, John: Sarcoma of the Uterus, Lancet **2:** 1246, 1937.

In a study of sarcoma of the uterus 40 cases are discussed. Sarcoma represents 1 per cent of the mesodermal tumors of the uterus reviewed and 2 per cent of the malignant tumors of the uterus. Treatment advised consists of a panhysterectomy with wide excision and the simultaneous removal of both appendages. This should be followed by deep x-ray therapy in all cases. Of 25 patients operated upon more than five years ago, 4 are alive and well, and one is alive but dying of a recurrence. The frequency of mitotic figures in a tumor is found to be the most reliable factor in the diagnosis. Little correlation between histologic cell type and prognosis could be demonstrated.

CARL P. HUBER.

Meigs, Joe V.: Cancer of the Ovary, New England J. Med. **220:** 545, 1939.

On the basis of 147 cases of ovarian cancer seen in the Massachusetts General Hospital during the years 1901 to 1933, the writer discusses origin, symptomatology and diagnosis, histopathology, and treatment of these neoplasms. This analysis leads him to the following conclusions: Ovarian cancer of the solid type always is very serious. The malignant papillary cystadenoma is about as malignant as any other epithelial growth. Early diagnosis is necessary for improvement of curative results, which are unsatisfactory and worse than those obtainable in cervical or mammary carcinoma. The use of the peritoneoscope should prove of great value in diagnosis. Bilateral oophorectomy with total hysterectomy is the operation to be carried out if possible. Its postoperative mortality is low. The rupture of cysts before or during operation and the use of the trocar cannot be proved dangerous by their end results, however, spilling of cyst contents always should be avoided. X-ray treatment to date has not proved of much curative value but more modern methods may still give better results. Every ovarian tumor that is removed should be opened before the surgeon ends his operation to rule out any suspicious papillary area.

HUGO EHRENFEST.

Mitra, Subodh: Carcinoma of the Cervix in India (the Five-Year End-Results), Brit. M. J. **1:** 747, 1937.

Malignant disease of the uterus is as common in India as it is elsewhere. A follow-up of the patients is very difficult, owing to economic, civic, and other factors. The author lists statistical studies of results with different methods of treatment. The comparative figures from the literature indicate that in the hands of experts the results of radiation therapy might be as good as those of operation, but in no case will they exceed them.

Interesting tables of the author's series of cases and those of others are presented.

F. L. ADAIR AND S. PEARL.

Smith, Frank Raymond: The Effect of Fractional Roentgen Technic on the Incidence of Vaginal Fistulae in Carcinoma of the Cervix, Radiology **30:** 748, 1938.

The incidence of vaginal fistulas in untreated cases of carcinoma of the cervix is more than twice as great as in treated patients. Vaginal fistulas are manifestations of progress of the disease rather than of injury by radiation.

A recent very low incidence of fistulas in the experience of the writer is attributed to a delay between the completion of roentgen therapy and local application of radium. At least one month should elapse between divided dose roentgen therapy and radium treatment; and at least two or three weeks when massive dosage is used.

S. D. SOULE.

Schroeder, R.: The Treatment of Cervical Carcinoma, Zentralbl. f. Gynäk. **61:** 546, 1937.

Schröder reviews the results of treatment of cervical carcinoma during a period slightly more than ten years in the Gynecological Clinic in Kiel. He followed up 604 patients who have been treated for a period longer than five years. Of these 171 (28 per cent) were classified as cases of absolute cure. The operable cases (58 per cent) were divided into four groups, (1) early, (2) endophytic, (3) exophytic, and (4) with deeper nodules.

Operation was undertaken in 302 cases, or 50 per cent; 178 patients were treated by Wertheim's method, with a primary mortality of 18 per cent, which with Schauta's operation amounted only to 1.5 per cent. The cure rate following Wertheim's operation was 36 per cent and that following Schauta's operation

was 51 per cent. Radium therapy was used in 253 cases, of which 51 were operable. One of these patients died at the beginning of treatment, and 21 (42 per cent) were cured. Of the 202 inoperable cases, 21 were alive after five years, i.e. 10 per cent; the immediate mortality was 18, or 8.5 per cent. Of all patients, operable and inoperable, treated with radium 42 (16.5 per cent) were living after five years. The immediate mortality was 19 (7.5 per cent). Latterly the immedaite mortality has been lessened and is now about 4 per cent for those treated with radium.

J. P. GREENHILL.

League of Nations: Annual Report on the Results of Radiotherapy in Cancer of the Uterine Cervix, Acta. obst. et gynec. Scandinav. **18**: Supplement II, 1938.

This is the second report issued by the League of Nations and includes analyses from nine radiotherapeutic centers throughout the world (U. S. A. (2), Brussels (1), England (3), France (2), and Sweden (1)). Information was collected concerning 6,570 patients who had cancer of the cervix. Of this number 5,672 (86.2 per cent) had radiotherapy. The results after five years were as follows:

Alive without recurrence	26.3 per cent
Alive with recurrence	1.8 per cent
Died of cancer	68.8 per cent
Died of intercurrent disease	2.0 per cent
Lost sight of	1.1 per cent

The 5,672 women were grouped as follows:

Stage I	10.7 per cent
Stage II	28.7 per cent
Stage III	42.6 per cent
Stage IV	18.0 per cent
Unclassified	0.04 per cent

The results of treatment for each group was as follows:

	RELATIVE CURE RATE
Stage I	55.2 per cent
Stage II	36.3 per cent
Stage III	21.2 per cent
Stage IV	5.3 per cent
Unclassified	0.0 per cent

Total Relative Cure Rate 26.3 per cent

J. P. GREENHILL.

Shaw, William Fletcher: Radium Versus Wertheim's Hysterectomy in the Treatment of Carcinoma of the Cervix, Surg. Gynec. Obst. **64**: 332, 1937.

It appears that we are getting at least the same percentage of cure with the use of radium as with Wertheim's operation, but with this great difference, that the radium cases include advanced as well as early ones, while the operation list necessarily includes only those in the first two stages.

Even if the results with radium were just as good as, but no better than, those with the operation, radium would be the treatment of choice. There is such a slight mortality and, what is almost of more importance, the convalescence is painless, whereas after Wertheim's operation a large percentage of the patients are very ill for some days, and at best are very slow in recovering from such a heavy strain.

WILLIAM C. HENSKE.

Keller, R.: Drainage and Thrombosis, Bull. Soc. d'obst. et de gynéc. **26**: 253, 1937.

In a series of 60 Wertheim operations performed for carcinoma of the cervix, the author encountered only two cases of postoperative thrombosis. This is

striking because in the author's clinic there is a far greater incidence of postoperative thrombosis even after simple operations. He attributes the infrequency of this complication in his Wertheim operations to the routine use of Mickulicz drains. They drain both abdominally and vaginally and traverse the entire field of operation. They assure complete removal of all secretions from the wound and hence prevent contaminating the field of operation. Furthermore the Mickulicz drain favors adhesions between the upper end of the wound and the omentum and intestines. These adhesions permit small engorged blood vessels to grow into the operative field, and they set up an active circulation and hence prevent the venous stasis which favors thrombosis. The author does not want to conclude that every operative case should be drained, yet he calls attention to the report by Gosset in which the latter claims unusual results following drainage after all his operations for fibroids.

J. P. GREENHILL.

Holterman, C.: Skin Metastases in Cases of Genital Carcinoma and Their Treatment, Ztschr. f. Geburtsh. u. Gynäk. **114:** 350, 1937.

The writer calls attention to a striking increase in skin metastases noticed in recent years in cases of carcinoma of the genitalia. In the Cologne University Woman's Clinic the author observed many cases of skin metastases. He believes this is due to the fact that with improved methods of treatment, patients live longer than formerly, and there is more time for the development of such metastases. The treatment is purely local. The author prefers surgery to radiation. In not a single instance where he removed the skin metastases surgically has there been a recurrence. The author, however, advocates postoperative radium treatment of the surgical scar. The prognosis of skin metastases is better than is generally supposed.

J. P. GREENHILL.

Jonsell, S.: Observations on Vaginal Metastases in Carcinoma of the Cervix Uteri at Radiumhemmet, Acta Radiologica **18:** 607, 1937.

This study is based on 1,881 cases of cervical cancer examined at Radiumhemmet (Stockholm) from 1914 to 1930. At the first examination vaginal metastases were found in 5.3 per cent of the series. In patients already treated, they developed in 7.5 per cent. Metastases in the upper half of the vagina before treatment do not seem to impair the prognosis. Metastases in the lower parts of the vagina as a rule occur in advanced cases. Vaginal metastases in cases already radiologically treated are ominous and associated with the appearance of other recurrences. In a few cases, where vaginal metastases were the only sign of cancer, permanent healing was obtained through renewed treatment.

J. P. GREENHILL.

Todd, T. F.: The Pathways and Relief of Pain in Advanced Carcinoma of the Cervix Uteri, Lancet **2:** 555, 1937.

Somatic and visceral are the two types of pain encountered in malignancy of the cervix. Somatic pain is prone to occur in neglected and untreated cases. It is experienced in the legs and thighs due to involvement of the afferent paths to these areas. The visceral pain is localized in the lower abdomen and pelvis, typically diffuse. Occasionally both types are observed in the same patient.

Treatment directed at symptomatic relief may be administered only after adequate evaluation. The pain must prevent sleep and the patient must be willing to undergo the procedure.

The cause must be accurately determined lest failure result. The autonomic nerve fibers are accessible in the parasympathetic plexus, while the peripheral nerves transverse the pelvis in the femoral, genitofemoral, lateral cutaneous, obturator, fifth lumbar, sacral, pudic, and coccygeal nerves.

The author treated all 11 cases of visceral pain by presacral neurectomy with complete success. The somatic pain should be best relieved by intrathecal alcoholic injections or cordotomy. The lumbar puncture is ordinarily made in one of the upper lumbar spaces. The motor fibers are not equally affected.

The etiology is discussed.

It is stressed that when appropriate treatment fails to relieve pain the patient is entitled to comfort without becoming an addict to morphine. It is emphasized that there will be failure in pain relief unless the appropriate treatment is given. This necessitates an accurate diagnosis of the type of pain.

H. CLOSE HESSELTINE.

Binet, A.: Analgesic Medication for Inoperable. Cancer of the Uterus and the Tolerance of the Organism for Morphin, Bull. Soc. d'obst. et de gynéc. **26:** 341, 1937.

In spite of the recent advances in the treatment of carcinoma of the uterus, a large proportion of women with such cancers suffer excruciating pain. The usual analgesics, such as aspirin and pyramidon, have only a momentary effect so that morphine must be used to secure any relief. Attempts are being made to avoid this by surgical, physiotherapeutic, and even biologic means, but they have not yet succeeded in replacing morphine. In a recent case of inoperable cancer Binet performed a resection of the superior hypogastric plexus with excellent results. Other operative procedures are chordotomy and lumbar ramisections. Cobra venom has also been suggested and tried by the author, but his patients did not obtain any relief from pain and cried for morphine. The chief drawback of morphine is the tolerance which patients develop. This occurs rapidly. The author reports a case where a patient gave herself 60 hypodermic injections of 0.02 cm. of morphine every day. This is the equivalent of 120 ordinary hypodermic doses of morphine.

J. P. GREENHILL.

Curtillet, E.: The Treatment of Pain in Cancer of the Cervix, Rev. franç. de gynéc. et d'obst. **32:** 306, 1937.

The author points out that morphine is generally employed to relieve the pain which is associated with cancer of the cervix. However, it is unsatisfactory because it weakens the patient, and produces a condition of stupor, it is temporary and costly, and the patient continues to suffer more or less between injections. Another medical measure to relieve this type of pain is cobra venom, but the failures with this substance are more frequent than the successes.

Among the surgical procedures recommended to relieve this type of pain are the following:

1. Section of the posterior roots of the lumbar nerves. This operation is now seldom performed.

2. Section or resection of the sympathetics. The chief operations in this class are hypogastric periarterial sympathectomy.

3. Medullary interventions of which cordotomy is the most common. The results are not very satisfactory.

4. Injections of alcohol.

The author recommends that the first procedure to be tried is subarachnoid injection of alcohol, because it is the simplest. If this fails, the superior hypogastric plexus should be resected if the patient's condition permits. If, however, this operation cannot be done or if the pain is sacral or renal in origin, a cordotomy will have to be done.

J. P. GREENHILL.

ROSTER OF AMERICAN OBSTETRICAL AND GYNECOLOGICAL SOCIETIES*

(Appears in January, April, July, October)

American Gynecological Society. *President,* F. L. Adair. *Secretary,* Richard W. TeLinde, 11 East Chase Street, Baltimore, Md. Next meeting, June 17-19, 1940, at the Seignory Club, Quebec, Canada.

American Association of Obstetricians, Gynecologists and Abdominal Surgeons. *President,* James R. McCord. *Secretary,* James R. Bloss, 418 11th Street, Huntington, W. Va. Next meeting, September 19 to 21, 1940, Excelsior Springs, Mo.

Central Association of Obstetricians and Gynecologists. *President,* Ralph A. Reis. *Secretary-Treasurer,* W. F. Mengert, Iowa City, Iowa. Annual meeting, Indianapolis, Ind., October, 1940.

South Atlantic Association of Obstetricians and Gynecologists. *President,* Robert E. Seibels. *Secretary,* Robert A. Ross, Durham, N. C. Next meeting, February 9 to 10, 1940, Richmond, Va.

A. M. A. Section on Obstetrics and Gynecology. *Chairman,* Ludwig A. Emge. *Secretary,* Norman F. Miller, Ann Arbor, Mich. Next meeting, June, 1940, New York City.

New York Obstetrical Society. *President,* William S. Smith. *Secretary,* Henry T. Burns, 162 East 71st St., New York City. Second Tuesday, from October to May, Yale Club.

Obstetrical Society of Philadelphia. *President,* Thomas B. Lee. *Secretary,* John C. Hirst, 500 North 20th St., Philadelphia, Pa. First Thursday, from October to May.

Chicago Gynecological Society. *President,* Julius E. Lackner. *Secretary,* Edward Allen, 55 East Washington St., Chicago, Ill. Third Friday, from October to June, Hotel Knickerbocker.

Brooklyn Gynecological Society. *President,* Goerge H. Davis. *Secretary,* Bruce A. Harris, 175 Clinton St., Brooklyn, N. Y. First Friday, from October to May, Kings County Medical Society, 1313 Bedford Avenue.

Baltimore Obstetrical and Gynecological Society. *President,* J. J. Eastman. *Secretary,* Frank K. Morris, 11 East Chase St., Baltimore, Md. Meets quarterly at Maryland Chirurgical Faculty Building.

Cincinnati Obstetrical Society. *President,* E. W. Enz. *Secretary,* Edward Friedman, 19 West Seventh St., Cincinnati, O. Third Thursday of each month.

Louisville Obstetrical and Gynecological Society. *President,* Esther C. Wallner. *Secretary,* Samuel S. Gordon, 520 Heyburn Building, Louisville, Ky. Fourth Monday, from September to May, Brown Hotel.

Portland Society of Obstetrics and Gynecology. *President,* Howard Stearns. *Secretary,* William M. Wilson, 545 Medical Arts Bldg., Portland, Ore. Last Wednesday of each month.

Pittsburgh Obstetrical and Gynecological Society. *President,* S. A. Chalfant. *Secretary,* Dr. Joseph A. Hepp, 121 University Place, Pittsburgh, Pa.

Obstetrical Society of Boston. *President,* Raymond S. Titus. *Secretary,* Judson A. Smith, 262 Beacon St., Boston, Mass. Third Tuesday, October to March, Harvard Club.

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*Changes, omissions, and corrections should be addressed to the Editor of the JOURNAL.

New England Obstetrical and Gynecological Society. *President,* Thomas Almy. *Secretary,* R. J. Heffernan, 475 Commonwealth Avenue, Boston, Mass. May and December.

Pacific Coast Obstetrical and Gynecological Society. *President,* Alice F. Maxwell. *President-Elect,* John Vruwink. Meetings held in late fall or early winter, rotating in the larger cities of the Pacific Coast.

Washington Gynecological Society. *President,* H. P. Ramsey. *Secretary,* James R. Costello, 900 17th Street, N. W., Washington, D. C. Fourth Saturday, October to May.

New Orleans Obstetrical and Gynecological Society. *President,* H. C. McGee. *Secretary,* H. W. Reddock, 1430 Tulane Avenue, New Orleans, La. Meetings held every other month.

St. Louis Gynecological Society. *President,* Percy H. Swahlen. *Secretary,* Joseph A. Hardy, Jr., 3720 Washington Blvd. Second Thursday, October, December, February, and April.

San Francisco Gynecological Society. *President,* T. Floyd Bell. *Secretary,* R. Glenn Craig, 490 Post Street, San Francisco, Calif. Regular meetings held second Friday in month, University Club, San Francisco, or Claremont Country Club, Oakland, Calif.

Item

American Board of Obstetrics and Gynecology

The general oral and pathological examinations (Part II) for all candidates (Groups A and B) will be conducted by the entire Board, meeting in Atlantic City, N. J., on June 8, 9, 10, and 11, 1940, immediately prior to the annual meeting of the American Medical Association in New York City.

Application for admission to Group A, Part II, examinations must be on file in the Secretary's Office not later than March 15, 1940. Formal notice of the time and place of these examinations will be sent each candidate several weeks in advance of the examination dates. Group A, Part II, candidates will be examined on June 8 and 9, and Group B, Part II, on June 10 and 11, 1940.

The annual dinner of the Board will be held in New York City on Wednesday evening, June 12, 1940, at the Hotel McAlpin.

For further information and application blanks, address Dr. Paul Titus, Secretary, 1015 Highland Building, Pittsburgh, (6) Pa.

Erratum

In the article by Dr. Theodore Neustaedter, "The Effect of Ingested Estrone (Progynon DH) and Parenterally Administered Synthetic Progestin (Proluton) Upon the Human Castrate Uterus," page 609, October, 1939 issue, the title should read: "The Effect of Ingested Alpha Estradiol . . ." instead of "The Effect of Ingested Estrone. . . ."